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Shū Kobayashi
Karl Anker Jørgensen (Eds.)
Cycloaddition Reactions in Organic Synthesis

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Introduction

Creation is wonderful. We admire Nature's work first – from simple things such as the hoar frost that settled overnight on the red maples, to the most intricate creation, repeated thousands of times each day, a human infant brought to term and born [1].

We admire human creation second – The Beatles and Bob Dylan, heroes from the sixties whose music and lyrics changed a whole generation. In the twenties Pablo Picasso and Paul Klee were among the artists who changed our conception of art.

Chemists make molecules, and synthesis is a remarkable activity at the heart of chemistry, this puts chemistry close to art. We create molecules, study their properties, form theories about why they are stable, and try to discover how they react. But at our heart is the molecule that is made, either by a natural process or by a human being [1].

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Cycloaddition reactions are close to the heart of many chemists – these reactions have fascinated the chemical community for generations. In a series of communications in the sixties, Woodward and Hoffmann [2] laid down the fundamental basis for the theoretical treatment of all concerted reactions. The basic principle enunciated was that reactions occur readily when there is congruence between the orbital symmetry characteristics of reactants and products, and only with difficulty when that congruence is absent – or to put it more succinctly, orbital symmetry is conserved in concerted reactions [3].

The development of the Woodward-Hoffmann rules in the sixties had a "natural link" to the famous papers published by Otto Diels and Kurt Alder. In a remarkable unpublished lecture delivered by Woodward to the American Chemical Society in Chicago on 28 August, 1973, on the occasion of the first Arthur Cope award to Woodward and Hoffmann, Woodward stated that when he was still only eleven years old he became aware through references in chemical textbooks, which he began to read in Boston Public Library, of the existence of journals which regularly published results of chemical research [4]. Woodward accordingly got in touch with the German Consul-General in Boston, Baron von Tippelskirch and through him obtained the main German periodicals *Berichte der deutschen Chemischen Gesellschaft, Journal für practische Chemie*, and *Justus Liebigs Annalen der Chemie* [5]. The specimen of the last-named, happened to be the first issue of

1928 and contained the famous papers published by Diels and Alder announcing their discovery of the cycloaddition involving alkenes and dienes, now known as the Diels-Alder reaction. The Diels-Alder paper fascinated Woodward who claimed that before reading the paper he had concluded that such a reaction must occur if one were to explain the separate existence – however transient – of the two Kekulé forms of benzene.

When Diels and Alder published their famous paper in 1928, Diels had been working with related reactions for several years [6]. In 1925, Diels reported the reaction of azodicarboxylic ester ($EtOC(O)_2CN{=}NC(O)OEt$) with compounds containing a conjugated diene system. He found that addition of the azodicarboxylic ester occurs at the 1,4-position of the conjugated system as with cyclopentadiene and with butadiene. This work probably led to the famous Diels-Alder reaction. In 1927, Diels and his student Alder published a paper on the reaction of azodicarboxylic ester with styrene.

The reaction investigated by Diels and Alder in 1928 was not new, examples had been known for several years [6]. Early work on the dimerization of tetrachloropentadienone was conducted by Zincke in 1893 and 1897. In 1906, Albrecht described the product of addition of *p*-benzoquinone to one or two molecules of cyclopentadiene. Albrecht assigned erroneous formulas to these addition products, but they were later shown to be typical products of the diene synthesis by Diels and Alder. Ruler and Josephson reported the addition products formed by isoprene and 1,4-benzoquinone in 1920. This research laid the ground work for Diels and Alder.

The basis of the Diels-Alder reaction developed in the twenties, and the contribution by Woodward and Hoffmann in the sixties, are two very important milestones in chemistry. Both discoveries were met with widespread interest; the applications made are fundamental to modern society; the tests which it has survived and the corollary predictions which have been verified are impressive.

We are now standing in the middle of the next step of the development of cycloaddition reactions – catalytic and catalytic enantioselective versions. The last two decades have been important in catalysis – how can we increase the reaction rate, and the chemo-, regio, diastereo-, and enantioselectivity of cycloaddition reactions? Metal catalysis can meet all these requirements!

In this book we have tried to cover some interesting aspects of the development of metal-catalyzed reactions. Different aspects of the various types of cycloaddition reactions have been covered.

Catalytic asymmetric Diels-Alder reactions are presented by Hayashi, who takes as the starting point the synthetically useful breakthrough in 1979 by Koga et al. The various chiral Lewis acids which can catalyze the reaction of different dienophiles are presented. Closely related to the Diels-Alder reaction is the [3+2] carbocyclic cycloaddition of palladium trimethylenemethane with alkenes, discovered by Trost and Chan. In the second chapter Chan provides some brief background information about this class of cycloaddition reaction, but concentrates primarily on recent advances. The part of the book dealing with carbo-cycloaddition reactions is

completed with a comprehensive review, by Denmark and Beutner, of enantioselective [2+1] cyclopropanation reactions with zinc carbenoids.

Catalytic enantioselective hetero-Diels-Alder reactions are covered by the editors of the book. Chapter 4 is devoted to the development of hetero-Diels-Alder reactions of carbonyl compounds and activated carbonyl compounds catalyzed by many different chiral Lewis acids and Chapter 5 deals with the corresponding development of catalytic enantioselective aza-Diels-Alder reactions. Compared with carbo-Diels-Alder reactions, which have been known for more than a decade, the field of catalytic enantioselective hetero-Diels-Alder reactions of carbonyl compounds and imines (aza-Diels-Alder reactions) are very recent.

Gothelf presents in Chapter 6 a comprehensive review of metal-catalyzed 1,3-dipolar cycloaddition reactions, with the focus on the properties of different chiral Lewis-acid complexes. The general properties of a chiral aqua complex are presented in the next chapter by Kanamasa, who focuses on 1,3-dipolar cycloaddition reactions of nitrones, nitronates, and diazo compounds. The use of this complex as a highly efficient catalyst for carbo-Diels-Alder reactions and conjugate additions is also described.

In the final chapter one of the editors, tries to tie together the various metal-catalyzed reactions by theoretical calculations. The influence of the metal on the reaction course is described and compared with that of "conventional" reactions in the absence of a catalyst.

It is our hope that this book, besides being of interest to chemists in academia and industry who require an introduction to the field, an update, or a part of a coherent review to the field of metal-catalyzed cycloaddition reactions, will also be found stimulating by undergraduate and graduate students.

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Karl Anker Jørgensen and Shu Kobayashi, June 2001

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[1] R. Hoffmann, *The Same and Not the Same*, Columbia University Press, New York, 1995.

[2] (a) R. B. Woodward, R. Hoffmann, *J. Am. Chem. Soc.* **1965**, *87*, 395; (b) R. Hoffmann, R. B. Woodward, *J. Am. Chem. Soc.* **1965**, *87*, 2046; (c) R. B. Woodward, R. Hoffmann, *J. Am. Chem. Soc.* **1965**, *87*, 2511.

[3] R. B. Woodward, R. Hoffmann, in *The Conservation of Orbital Symmetry*, Verlag Chemie, Weinheim, 1970, p. 1.

[4] Part of this is taken from The Royal Society Biography of Robert Burns Woodward, written by Lord Todd and Sir John Cornforth, **1980**, p. 629.

[5] It has not been possible to obtain details about correspondence or contacts between Woodward and the German Consul-General Kurt Wilhelm Viktor von Tippelskirch, born in Ruppin in 1878, German Consul-General in Boston from 1926 to 1938, and who died in Siberia in Soviet internment in 1943 [4].

[6] See, e.g., Otto Paul Hermann Diels in *Nobel Laureate in Chemistry 1901–1992*, L. K. James (Ed.), American Chemical Society **1994**, p. 332.

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1
Catalytic Asymmetric Diels-Alder Reactions

Yujiro Hayashi

1.1
Introduction

The Diels-Alder reaction is one of the most useful synthetic reactions for the construction of the cyclohexane framework. Four contiguous stereogenic centers are created in a single operation, with the relative stereochemistry being defined by the usually *endo*-favoring transition state.

Asymmetric Diels-Alder reactions using a dienophile containing a chiral auxiliary were developed more than 20 years ago. Although the auxiliary-based Diels-Alder reaction is still important, it has two drawbacks – additional steps are necessary, first to introduce the chiral auxiliary into the starting material, and then to remove it after the reaction. At least an equimolar amount of the chiral auxiliary is, moreover, necessary. After the discovery that Lewis acids catalyze the Diels-Alder reaction, the introduction of chirality into such catalysts has been investigated. The Diels-Alder reaction utilizing a chiral Lewis acid is truly a practical synthetic transformation, not only because the products obtained are synthetically useful, but also because a catalytic amount of the chiral component can, in theory, produce a huge amount of the chiral product.

The first synthetically useful breakthrough in the catalytic Diels-Alder reaction came with the work of Koga and coworkers reported in 1979 (vide infra) [1]. Since Koga's work, many chiral Lewis acids have been developed and applied to the Diels-Alder reaction. There are several good reviews of catalytic asymmetric Diels-Alder reactions utilizing a chiral Lewis acid [2], including Evans's excellent recent review [2a]. In most of these reviews, the Diels-Alder reactions are categorized according to the metal of the chiral Lewis acid. In general, the dienophiles used in the Diels-Alder reaction are categorized into two groups – those which bind to the Lewis acid at one point and those which bind at two points. α,β-Unsaturated aldehydes and esters belong to the first category; 3-alkenoyl-1,3-oxazolidin-2-ones (abbreviated to 3-alkenoyloxazolidinones), for instance, belong to the latter. This classification is, however, not always valid. For example, although 3-alkenoyloxazolidinone is a good bidentate ligand for most of the metals used, Corey's chiral aluminum catalyst activates acryloyloxazolidinone by binding at a single-point only (vide infra) [3]. Different tactics should be necessary for the development of chiral Le-

wis acids effective for each type of dienophile. In this review, Diels-Alder reactions are classified by dienophile type – α,β-unsaturated aldehydes, α,β-unsaturated esters, 3-alkenoyl-1,3-oxazolidin-2-ones, and others. The asymmetric Diels-Alder reaction is a rapidly expanding area and many interesting results have appeared. This review deals only with catalytic asymmetric homo-Diels-Alder reactions proceeding in an enantiomeric excess (ee) greater than 90%, which is the synthetically useful level.

1.2 The Chiral Lewis Acid-catalyzed Diels-Alder Reaction

1.2.1 The Asymmetric Diels-Alder Reaction of α,β-Unsaturated Aldehydes as Dienophiles

1.2.1.1 Aluminum

The pioneering work in the chiral Lewis-acid promoted Diels-Alder reaction was that of Koga, reported in 1979, in which the first catalytic asymmetric reaction proceeding in high enantioselectivity was realized [1] (Scheme 1.1). The catalyst **1**, prepared from $EtAlCl_2$ and menthol, was thought to be "menthoxyaluminum dichloride", and promoted the Diels-Alder reaction of methacrolein and cyclopentadiene in 72% ee. Although they went on to examine several chiral ligands containing the cyclohexyl moiety, higher enantioselectivity could not be achieved.

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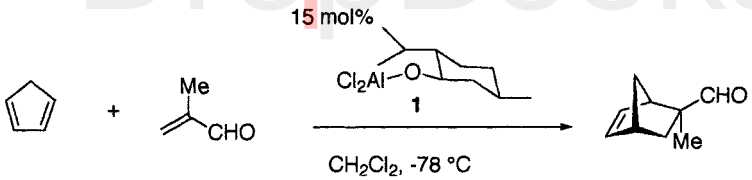
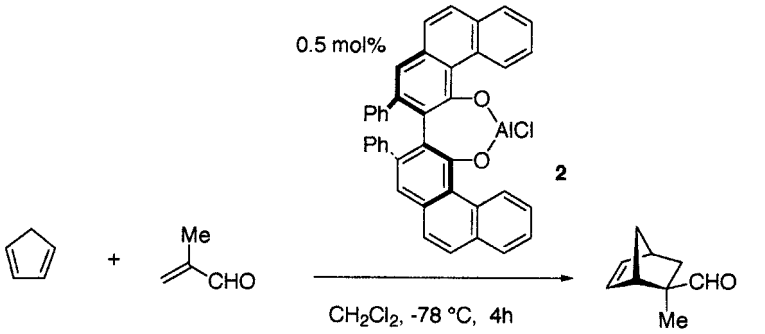


Scheme 1.1 72% ee, 69%, *endo:exo* = 2:98

Chiral aluminum catalyst **2**, prepared from Et_2AlCl and a "vaulted" biaryl ligand, is reported to be an effective Lewis acid catalyst of the Diels-Alder reaction between methacrolein and cyclopentadiene, affording the adduct in 97.7% ee [4] (Scheme 1.2). Although the Diels-Alder reaction with other α,β-unsaturated aldehydes has not been described, that only 0.5 mol% loading is sufficient to promote the reaction is a great advantage of this catalyst.

1.2.1.2 Boron

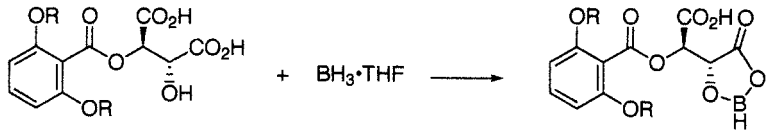
In 1989 Yamamoto et al. reported that the chiral (acyloxy)borane (CAB) complex **3** is effective in catalyzing the Diels-Alder reaction of a number of α,β-unsaturated aldehydes [5]. The catalyst was prepared from monoacylated tartaric acid and bo-



Scheme 1.2

97.7% ee, 100%, *endo*:*exo* = 3:97

rane-THF complex with the generation of H_2. The boron atom of the (acyloxy)borane is activated by the electron-withdrawing acyloxy group (Scheme 1.3).



Scheme 1.3

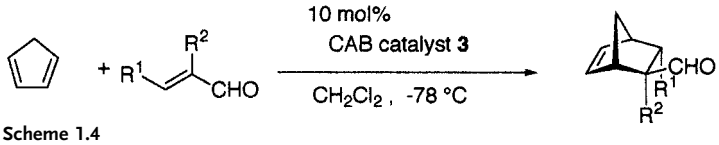
R = Me or *i*-Pr

3

The chiral (acyloxy)borane (CAB) catalyst **3** is a practical catalyst, because it is applicable to the reaction of a variety of dienes and aldehydes giving high enantioselectivity (Scheme 1.4, 1.5, Table 1.1, 1.2). The reaction has generality, working not only for reactive cyclopentadiene, but also for less reactive dienes like isoprene. There are several noteworthy features. An α-substituent on the dienophile increases enantioselectivity (acrolein relative to methacrolein), whereas β-substitution dramatically reduces it (crotonaldehyde). When the substrate has substituents at both α- and β-positions, high enantioselectivity is observed. In a series of investigations using several kinds of tartaric acid derivative, it was found that the boron atom can form a five-membered ring structure with an α-hydroxy acid moiety of the tartaric acid, and that the remaining carboxyl group may not bond to the boron atom.

One interesting phenomenon was the effect of the boron substituent on enantioselectivity. The stereochemistry of the reaction of α-substituted α,β-unsaturated aldehydes was completely independent of the steric features of the boron substituents, probably because of a preference for the *s-trans* conformation in the transition state in all cases. On the other hand, the stereochemistry of the reaction of cyclopentadiene with α-unsubstituted α,β-unsaturated aldehydes was dramatically reversed on altering the structure of the boron substituents, because the stable conformation changed from *s-cis* to *s-trans*, resulting in production of the opposite enantiomer. It should be noted that selective cycloadditions of α-unsubstituted α,β-unsaturated aldehydes are rarer than those of α-substituted α,β-unsatu-

rated aldehydes, because it is difficult to control the *s-cis*/*s-trans* conformation ratio of the former in the transition state, whereas for the latter the *s-trans* conformation predominates. These results indicate that control of the *s-cis*/*s-trans* conformation of the former aldehydes can be achieved by means of the catalyst.



Scheme 1.4

Table 1.1 Asymmetric Diels-Alder reactions of cyclopentadiene catalyzed by CAB catalyst **3** [5 a, b]

R^1	R^2	*Time (h)*	*Yield (%)*	*endo/exo*	*ee (%)*
H	Me	6	85	11:89	96
H	H	14.5	90	88:12	84
Me	H	10	53	90:10	2
Me	Me	9.5	91	3:97	90
H	Br	10	100	6:94	95
Me	Br	12	100	>1:99	98

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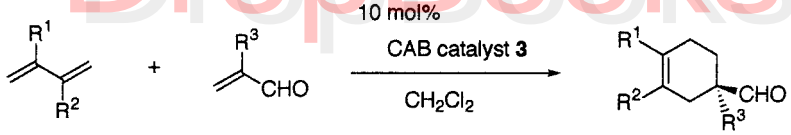


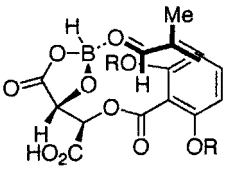
Scheme 1.5

Table 1.2 Asymmetric Diels-Alder reactions catalyzed by CAB catalyst **3** [5 a, b]

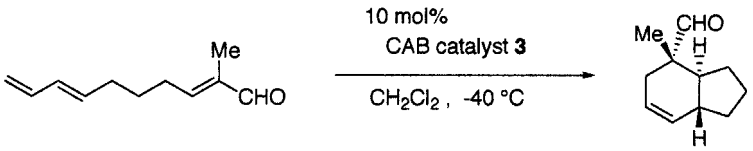
R^1	R^2	R^3	*Temp. (°C)*	*Time (h)*	*Yield (%)*	*ee (%)*
Me	Me	Me	–78	7.5	61	97
Me	H	Me	–40	10.5	65	91
Me	Me	H	–78	10.5	53	84
Me	Me	Br	–78	46	80	95
Me	H	Br	–40	12	52	87

A detailed ^{1}H NMR study and determination of the X-ray structure of the ligand has suggested the occurrence of π-stacking of the 2,6-diisopropoxybenzene ring and coordinated aldehyde [5 c]. Because of this stacking, the *si* face of the CAB-coordinated *α,β*-unsaturated aldehyde is sterically shielded (Fig. 1.1).

Fig. 1.1 CAB catalyst **3** and methacrolein



The intramolecular Diels-Alder reaction of 2-methyl-(*E,E*)-2,7,9-decatrienal catalyzed by the CBA catalyst **3** proceeds with the same high diastereo- and enantioselectivity [5d] (Scheme 1.6).

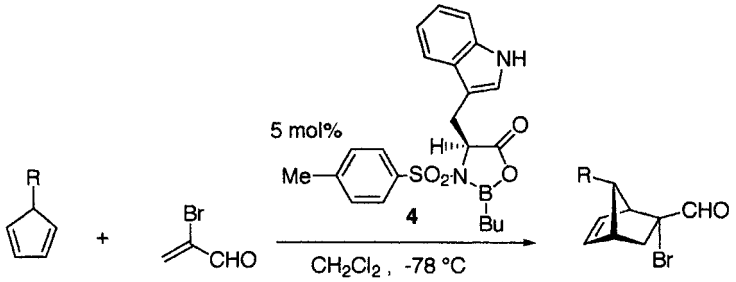


Scheme 1.6

92% ee, 84%, *endo:exo* = 99:1

A tryptophan-derived oxazaborolidine **4** was prepared by Corey et al. from a tryptophan derivative and $BuB(OH)_2$ with elimination of water [6]. In the first use of α-bromoacrolein in the catalytic asymmetric Diels-Alder reaction, Corey et al. applied this catalyst to α-bromoacrolein, a reaction which is outstandingly useful, because of the exceptional synthetic versatility of the resulting cycloadducts. Corey et al. have shown that the adduct of α-bromoacrolein and benzyloxymethylcyclopentadiene obtained in high optical purity can be transformed into an important intermediate for the synthesis of prostaglandins [6a] (Scheme 1.7, 1.8). Since this publication the Diels-Alder reaction of α-bromoacrolein and cyclopentadiene has come to be regarded as a test reaction of the effectiveness of newly developed chiral Lewis acids. Other applications of this asymmetric Diels-Alder reaction to natural product synthesis are shown in Schemes 1.7–1.11 [6c]. The Diels-Alder reaction of an elaborated triisopropoxydiene and methacrolein catalyzed by the modified borane reagent affords in high optical purity a chiral cyclohexane skeleton, which was successfully transformed to cassinol (Scheme 1.9). The chiral Diels-Alder adduct obtained in high optical purity (99% ee) from 2-(2-bromoallyl)-1,3-cyclopentadiene and α-bromoacrolein was converted to a key intermediate in the synthesis of the plant growth regulator gibberellic acid (Scheme 1.10).

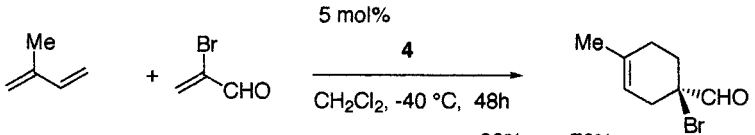
The structure of the complex of (*S*)-tryptophan-derived oxazaborolidine **4** and methacrolein has been investigated in detail by use of ^{1}H, ^{11}B and ^{13}C NMR [6b]. The proximity of the coordinated aldehyde and indole subunit in the complex is suggested by the appearance of a bright orange color at 210 K, caused by formation of a charge-transfer complex between the π-donor indole ring and the acceptor aldehyde. The intermediate is thought to be as shown in Fig. 1.2, in which the *s-cis* conformer is the reactive one.



R = H: 1h, 99% ee, 95%, *endo:exo* = 4:96

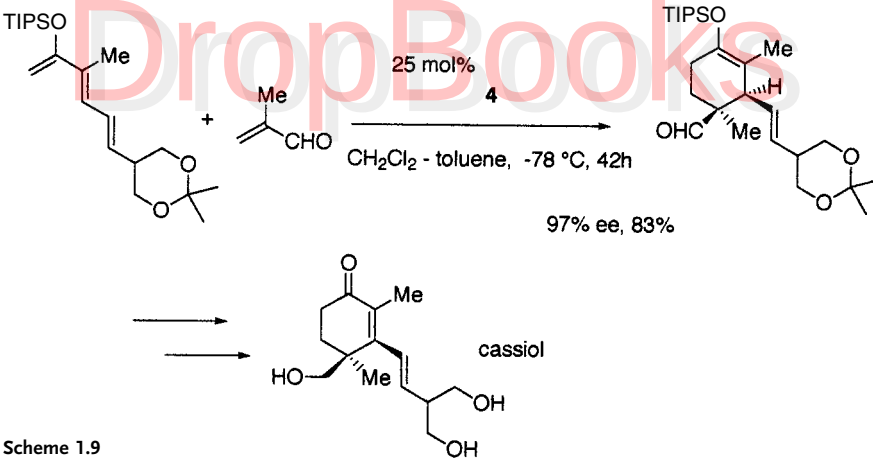
R = CH_2OBn: 8h, 92% ee, 81-83%, *endo:exo* = 5:95

Scheme 1.7



92% ee, 76%

Scheme 1.8



97% ee, 83%

Scheme 1.9

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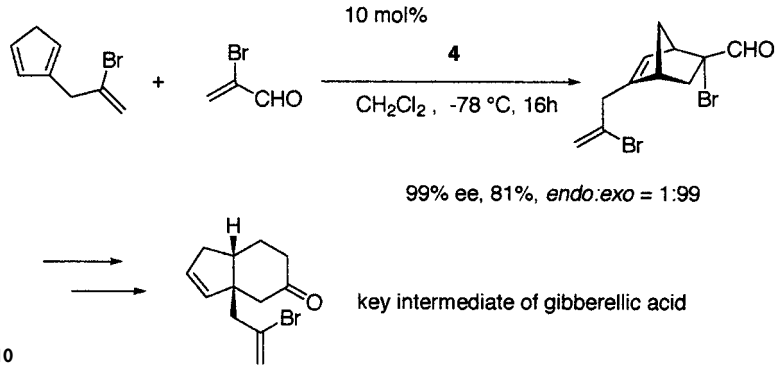
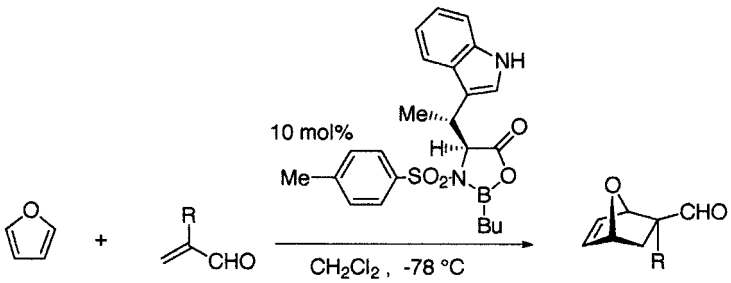
The borane catalyst **4** is also effective in the Diels-Alder reaction of furan (Scheme 1.11). In the presence of a catalytic amount of this reagent *α*-bromoacrolein or *α*-chloroacrolein reacts with furan to give the cycloadduct in very good chemical yield with high optical purity [6 d].

The polymer-supported chiral oxazaborolidinone catalyst **5** prepared from valine was found by Ituno and coworkers to be a practical catalyst of the asymmetric Diels-Alder reaction [7] (Scheme 1.12). Of the several cross-linked polymers with a



Scheme 1.10



Scheme 1.11

chiral *N*-sulfonylamino acid moiety examined, the polymeric catalyst containing a relatively long oxyethylene chain cross-linkage gave higher enantioselectivity than those with flexible alkylene chain cross-linkages or with shorter oxyethylene chain cross-linkages. An interesting feature is that this polymeric chiral catalyst is more enantioselective than its low-molecular-weight counterpart. One of the great synthetic advantages of this reaction is that catalyst **5** can be easily recovered from

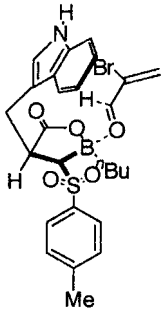
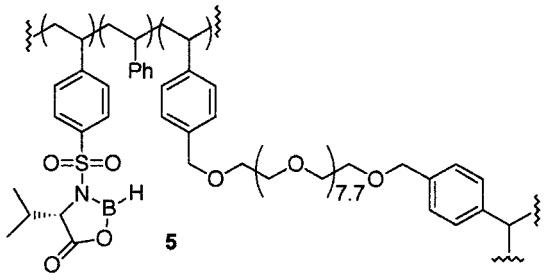
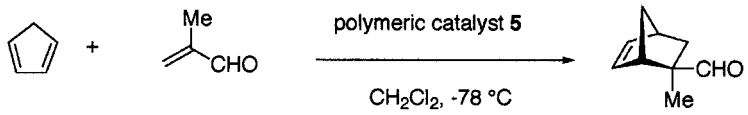


Fig. 1.2 Oxazaborolidine **4** and α-bromoacrolein

the products and re-used. The reaction can be performed in a flow system, which avoids destruction of the polymeric beads by vigorous stirring.



5



Scheme 1.12

95% ee, 88%, *endo:exo* = 4:96

Kobayashi and Mukaiyama developed a zwitterionic, proline-based Lewis acid **6** by mixing aminoalcohol and BBr_3 [8] (Scheme 1.13). The structure of the catalyst was determined by ^{11}B, ^{1}H, and ^{13}C NMR analysis [9]. The HBr salt is important for achieving high enantioselectivity – the catalyst prepared from the sodium salt of the aminoalcohol and BBr_3 (HBr-free condition) is ineffective, whereas the adduct was produced with high enantioselectivity when the catalyst prepared by reaction of aminoalcohol, NaH, BBr_3, and HBr gas was used. This catalyst promotes the Diels-Alder reaction of methacrolein and cyclopentadiene with high enantioselectivity.

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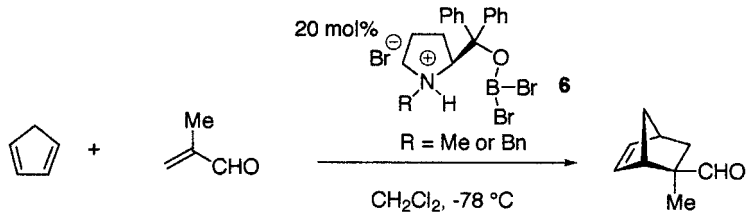
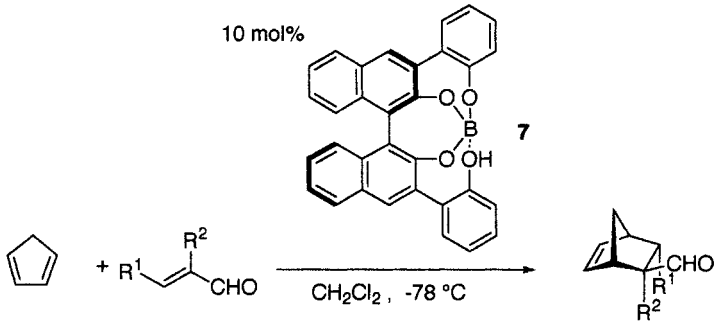


Scheme 1.13

97% ee, 84%, *endo:exo* = >1:99

In 1994 Yamamoto et al. developed a novel catalyst which they termed a "Brønsted acid-assisted chiral Lewis acid" (BLA) [10] (Scheme 1.14, Table 1.3). The catalyst **7** was prepared from (*R*)-3,3′-dihydroxyphenyl)-2,2′-dihydroxy-1,1′-binaphthyl by reaction with $B(OMe)_3$ and removal of methanol [10a,d]. The Brønsted acid is essential for both the high reactivity of the Lewis acid and the high enantioselectivity – the

borane catalyst prepared from the monobenzyl ether or monosilyl ether of the parent ligand afforded cycloadducts in only low chemical and optical yields. Although catalyst **7** is one of the best for the enantio- and *exo*-selective Diels-Alder reaction of α-substituted a,β-unsaturated aldehydes with highly reactive dienes such as cyclopentadiene, enantioselectivity is low for the corresponding reaction of α-unsubstituted a,β-unsaturated aldehydes such as acrolein and crotonaldehyde.

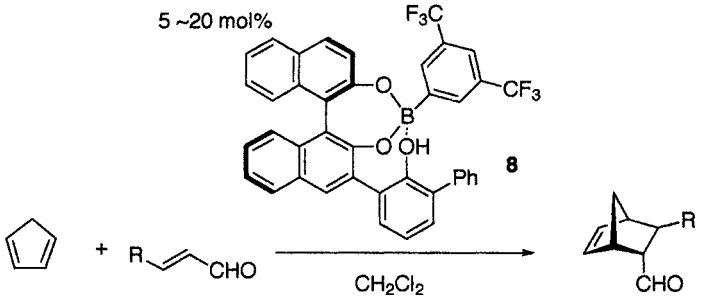


Scheme 1.14

Table 1.3 Asymmetric Diels-Alder reactions of α-substituted aldehydes catalyzed by **7** [10a, d]

R^1	R^2	*Yield (%)*	*endo/exo*	*ee (%)*
H	Br	>99	>1:99	99
H	Me	>99	>1:99	99
H	Et	>99	3:97	92
Me	Me	>99	>1:99	98
$-(CH_2)_3-$		>99	2:98	93

To overcome these problems with the first generation Brønsted acid-assisted chiral Lewis acid **7**, Yamamoto and coworkers developed in 1996 a second-generation catalyst **8** containing the 3,5-bis-(trifluoromethyl)phenylboronic acid moiety [10b, d] (Scheme 1.15, 1.16, Table 1.4, 1.5). The catalyst was prepared from a chiral triol containing a chiral binaphthol moiety and 3,5-bis-(trifluoromethyl)phenylboronic acid, with removal of water. This is a practical Diels-Alder catalyst, effective in catalyzing the reaction not only of α-substituted a,β-unsaturated aldehydes, but also of α-unsubstituted a,β-unsaturated aldehydes. In each reaction, the adducts were formed in high yields and with excellent enantioselectivity. It also promotes the reaction with less reactive dienophiles such as crotonaldehyde. Less reactive dienes such as isoprene and cyclohexadiene can, moreover, also be successfully employed in reactions with bromoacrolein, methacrolein, and acrolein dienophiles. The chiral ligand was readily recovered (>90%).



Scheme 1.15

Table 1.4 Asymmetric Diels-Alder reactions of α-unsubstituted aldehydes catalyzed by **8** [10b, d]

R	*Temp. (°C)*	*Yield (%)*	*endo/exo*	*ee (%)*
H	–78	84	97 : 3	95
Me	–78	94	90 : 10	95
Et	–78	73	91 : 9	98
Ph	–40	94	74 : 26	80
CO_2Et	–78	91	98 : 2	95

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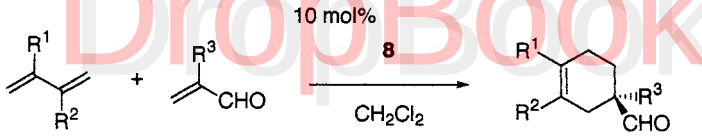
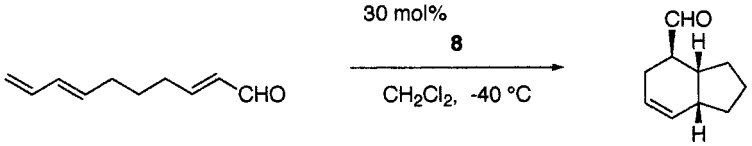


Scheme 1.16

Table 1.5 Asymmetric Diels-Alder reactions catalyzed by **8** [10d]

R^1	R^2	R^3	*Yield (%)*	*ee (%)*
Me	H	Br	95	>99
Me	Me	Br	95	91
Me	H	Me	73	>99
Me	H	H	95	99
Me	Me	H	97	>99

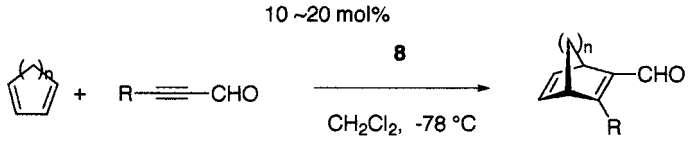
Brønsted acid-assisted chiral Lewis acid **8** was also applied to the intramolecular Diels-Alder reaction of an α-unsubstituted triene derivative. (*E,E*)-2,7,9-Decatrienal reacts in the presence of 30 mol% of the catalyst to afford the bicyclo compound in high yield and good enantioselectivity [10d] (Scheme 1.17).



Scheme 1.17

80% ee, 95%, *endo:exo* = >99:1

Another application of catalyst **8** is to the reaction of acetylenic aldehydes [10c] (Scheme 1.18, Table 1.6). Two acetylenic dienophiles have been reacted with cyclopentadiene or cyclohexadiene to give bicyclo[2.2.1]heptadiene or bicyclo[2.2.2]octadiene derivatives in high optical purity. A theoretical study suggests that this reaction proceeds via an *exo* transition state.



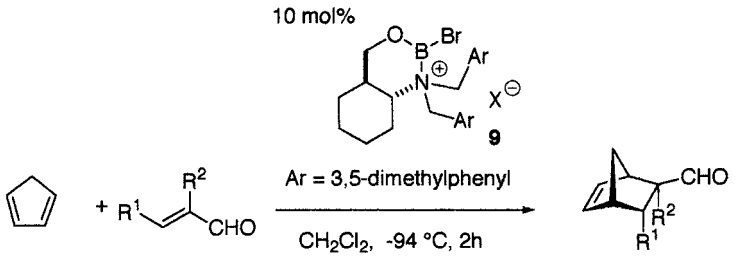
Scheme 1.18

Table 1.6 Asymmetric Diels-Alder reactions of alkynyl aldehydes catalyzed by **8** [10c]

R	*n*	*Yield (%)*	*ee (%)*
H	1	63	88
CO_2Et	1	97	95
CO_2Et	2	81	84
I	1	72	85

For many of these asymmetric Diels-Alder reactions, there are major limitations with regard to the range of dienes to which they can be applied successfully. In most asymmetric catalytic Diels-Alder reactions with *a,β*-unsaturated aldehydes as dienophiles, reactive dienes such as cyclopentadiene have been employed, and 1,3-butadiene and 1,3-cyclohexadiene have not been used successfully. To expand the scope and utility of the catalytic enantioselective Diels-Alder reaction, Corey and coworkers have developed a new class of super-reactive chiral Lewis acid catalyst [11] (Scheme 1.19, 1,20, Table 1.7). Cationic oxazaborinane catalyst **9** was prepared from aminosilyl ether and BBr_3. As the same high enantioselectivity was obtained with a molar ratio of BBr_3 to aminosilyl ether between 0.9:1 and 1.6:1, the cationic form of **9** (paired with the BBr_4^- counter-ion) is thought to be generated. A much more active Lewis acid catalyst was generated on addition of $Ag^+B[C_6H_3\text{-}3,5\text{-}(CF_3)_2]_4^-$ to the above catalyst; this afforded the super-reactive catalyst with the $B[C_6H_3\text{-}3,5\text{-}(CF_3)_2]_4^-$ counter-ion. In the presence of this catalyst *α*-substituted *a,β*-unsaturated aldehydes react not only with reactive cyclopentadiene, but also 1,3-

butadiene and 1,3-cyclohexadiene at low temperature (–94 °C), in short reaction times (<2 h), to afford cycloadducts with high *exo* and enantioselectivity.



Scheme 1.19

Table 1.7 Asymmetric Diels-Alder reactions catalyzed by super Lewis acid **9** [11]

R^1	R^2	X	Yield (%)	endo/exo	ee (%)
H	Br	$B[C_6H_3\text{-}3,5\text{-}(CF_3)_2]_4$	99	9:91	98
H	Br	Br or BBr_4	99	6:94	95
H	Me	$B[C_6H_3\text{-}35\text{-}(CIF_3)_2]_4$	98	11:89	87
H	Me	Br or BBr_4	99	12:82	90
Me	Br	$B[C_6H_3\text{-}3,5\text{-}(CF_3)_2]_4$	99	>2:98	96
Me	Me	Br or BBr_4	88	>2:98	89
$-(CH_2)_4-$		Br or BBr_4	99	>2:98	96

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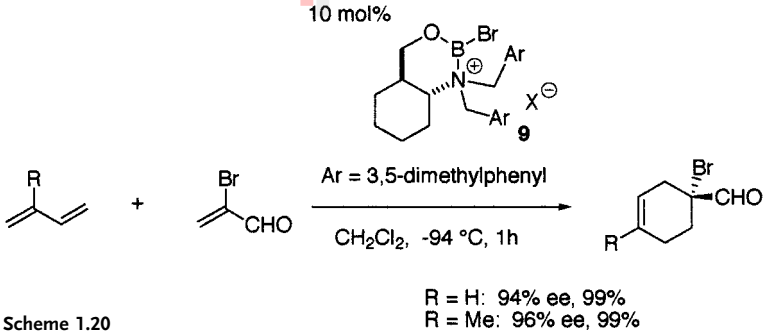
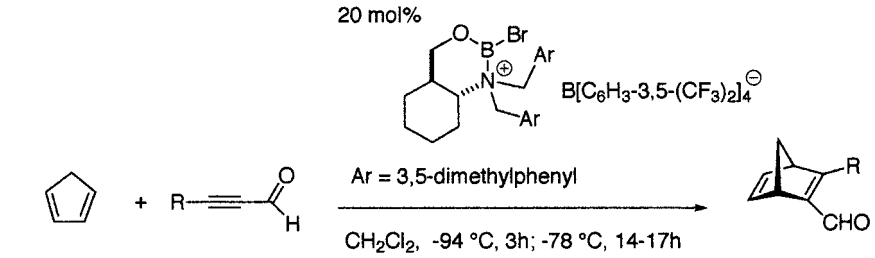


Scheme 1.20

This catalyst was successfully applied to the Diels-Alder reaction of propargyl aldehydes as dienophiles [12] (Scheme 1.21, Table 1.8). Though 2-butyn-1-al and 2-octyn-1-al are unreactive dienophiles, silyl- and stannyl-substituted *a,β*-acetylenic aldehydes react with cyclopentadiene readily in the presence of 20 mol% of the catalyst at low temperature to give bicyclo[2.2.1]heptadiene derivatives in high optical purity; these derivatives are synthetically useful chiral building blocks.

The two 3,5-dimethylbenzyl substituents on the nitrogen atom of the ligand are important determinants of the enantioselectivity. The reaction is thought to proceed



Scheme 1.21

Table 1.8 Asymmetric Diels-Alder reactions of alkynyl aldehydes catalyzed by **9** [12]

R	*Yield (%)*	*ee (%)*
Me_3Si	68	87
Et_3Si	37	85
Me_2PhSi	50	87
Bu_3Sn	83	80

as follows: one of the N-CH_2Ar substituents serves to block attack on the lower face of the *s-trans*-coordinated dienophile, whereas the other screens off another region in space and limits the rotation of both the dienophile and the other N-CH_2Ar group. In the transition state, the formyl hydrogen atom is placed in proximity to the oxygen substituent on the boron atom, and held there by a C–H$\cdots$O hydrogen bond to the equatorial oxygen lone pair (Fig. 1.3).

The formyl C–H$\cdots$O hydrogen bond idea (Fig. 1.4) was first conceived for the catalyst **9** and its existence is supported by several X-ray studies of $BX_3\cdot$aldehyde

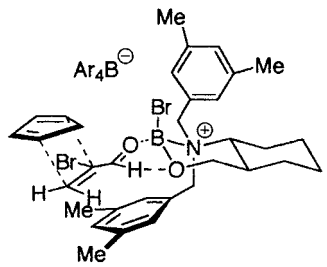


Fig. 1.3 Transition structure of the cationic oxazaborinane **9**

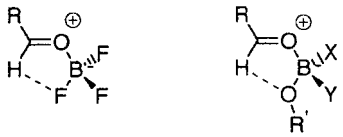


Fig. 1.4 Hydrogen bond of formyl CH

complexes performed by Corey and coworkers [13]. The X-ray crystal structures of the complexes $C_6H_5CHO \cdot BF_3$ [14], $H_2C{=}C(CH_3)CHO \cdot BF_3$ [15], and $DMF \cdot BX_3$ (X = F, Cl, Br, I) [13a] reveal:

(i) BX_3 is coordinated to the oxygen lone pair, which is *syn* to the formyl proton.
(ii) The carbonyl $\cdot BF_3$ complex prefers the eclipsed-coplanar B–F/formyl arrangement, but the complexes $DMF \cdot BX_3$ (X = Cl, Br, I) do not.
(iii) For carbonyl $\cdot BF_3$ complexes, the distance between the eclipsed H (formyl) and F (borane) is considerably less than the sum of the van der Waals radii.

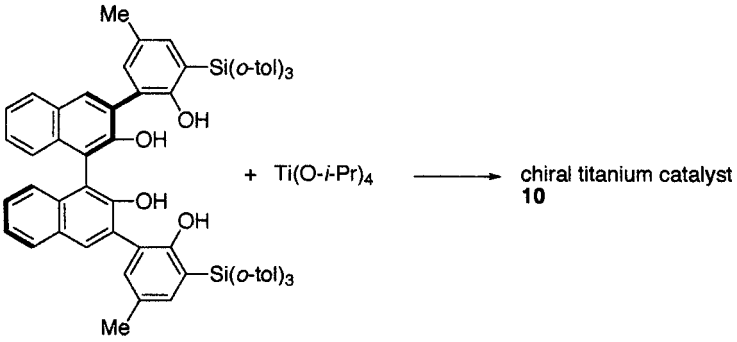
These results suggest an attractive interaction or weak hydrogen bond between the formyl proton and eclipsed fluorine. The X-ray crystal structure of the B-bromocatecholborane–DMF complex also suggests the occurrence of similar weak, attractive interaction, i.e. a hydrogen bond, between the formyl group and nearby oxygen. This novel hydrogen-bonding effect between a coordinated formyl and oxygen substituents at boron can be used to rationalize several enantioselective Diels-Alder reactions of chiral Lewis catalysts such as Corey's super-Lewis acidic catalyst **9** (vide supra), Corey's (*S*)-tryptophan derived borane **4**, Yamamoto's chiral acyloxyborane (CAB) **3**, Yamamoto's Brønsted acid-assisted chiral Lewis acids (BLA) **7** and **8**, Yamamoto's chiral helical titanium catalyst (vide infra) **10**, and Koga's menthoxyaluminum chloride **1** [13b,c].

DropBooks

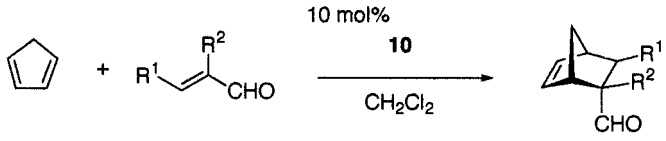
1.2.1.3 Titanium

Yamamoto et al. have reported a chiral helical titanium catalyst, **10**, prepared from a binaphthol-derived chiral tetraol and titanium tetraisopropoxide with azeotropic removal of 2-propanol [16] (Scheme 1.22, 1.23, Table 1.9). This is one of the few catalysts which promote the Diels-Alder reaction of *α*-unsubstituted aldehydes such as acrolein with high enantioselectivity. Acrolein reacts not only with cyclopentadiene but also 1,3-cyclohexadiene and 1-methoxy-1,3-cyclohexadiene to afford cycloadducts in 96, 81, and 98% ee, respectively. Another noteworthy feature of the titanium catalyst **10** is that the enantioselectivity is not greatly influenced by reaction temperature (96% ee at
–78 °C, 92% ee at –20 °C, 88% ee at 0 °C in the reaction of acrolein and cyclopentadiene). This is unusual for metal-catalyzed asymmetric reactions, with only few similar examples. The titanium catalyst **10** acts as a suitable chiral template for the conformational fixing of *α,β*-unsaturated aldehydes, thereby enabling efficient enantioface recognition, irrespective of temperature.

Another chiral titanium reagent, **11**, was developed by Corey et al. [17] (Scheme 1.24). The catalyst was prepared from chiral *cis-N*-sulfonyl-2-amino-1-indanol and titanium tetraisopropoxide with removal of 2-propanol, followed by treatment with one equivalent of $SiCl_4$, to give the catalytically-active yellow solid. This catalyst is thought not to be a simple monomer, but rather an aggregated species, as suggested by ^1H NMR study. Catalyst **11** promotes the Diels-Alder reaction of *α*-bromoacrolein with cyclopentadiene or isoprene.



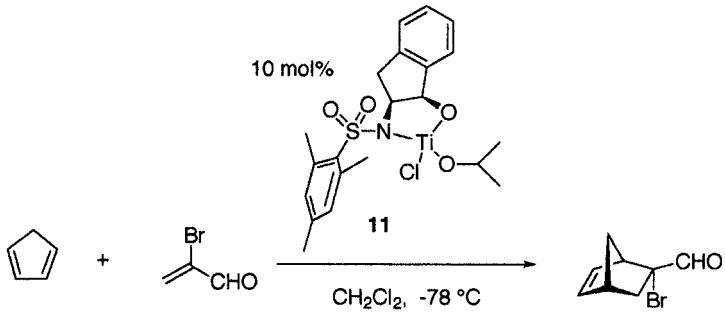
Scheme 1.22



Scheme 1.23

Table 1.9 Asymmetric Diels-Alder reactions of cyclopentadiene catalyzed by **10** [16]

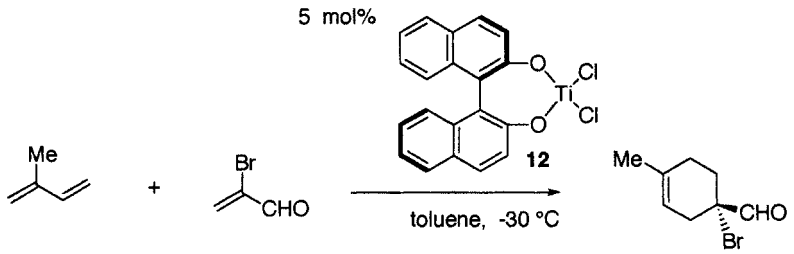
R^1	R^2	Temp. (°C)	Time (h)	Yield (%)	endo/exo	ee (%)
H	H	–78	3.5	70	85:15	96
Me	H	–40	50	76	70:30	95
H	Me	–78	70	75	1:99	94(*S*)



Scheme 1.24

93% ee, 94%, *endo:exo* = 1:67

Mikami et al. have reported that the chiral titanium reagent **12** derived from binaphthol and $TiCl_2(O\text{-}i\text{-}Pr)_2$ catalyzes the Diels-Alder reaction of α-bromoacrolein or methacrolein with isoprene or 1-methoxy-1,3-butadiene to afford the cycloadducts with high enantioselectivity [18] (Scheme 1.25).



Scheme 1.25

1.2.1.4 Iron

Kündig and coworkers have developed a cationic Cp iron(II) complex **13** containing the 1,2-(bis(pentafluorophenyl)phosphanyl)cyclopentane or diphenyl ethane moiety as ligand [19] (Scheme 1.26, Table 1.10). The catalyst **13** was prepared by reacting $CpFeMe(CO)_2$ with the appropriate fluorophenyl ligand under irradiation, followed by treatment with HBF_4. The Diels-Alder reaction is performed in the presence of 2,6-di-*tert*-butylpyridine to inhibit a competing reaction resulting from an achiral Lewis acid. Though the cationic chiral iron catalyst **13** is not thermally stable (it decomposes slowly above –20 °C), in its presence *α*-bromoacrolein reacts with both reactive and unreactive dienes such as cyclohexadiene, giving adducts in good optical purity (>95% ee).

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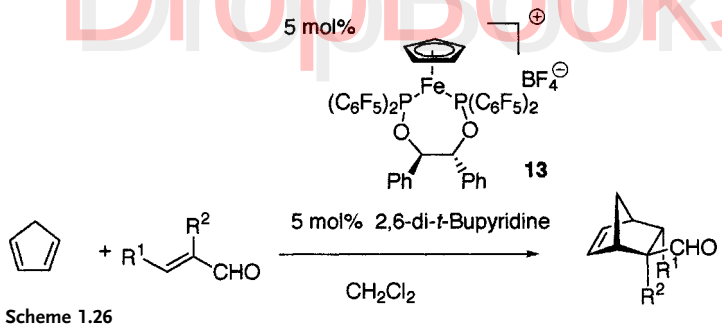


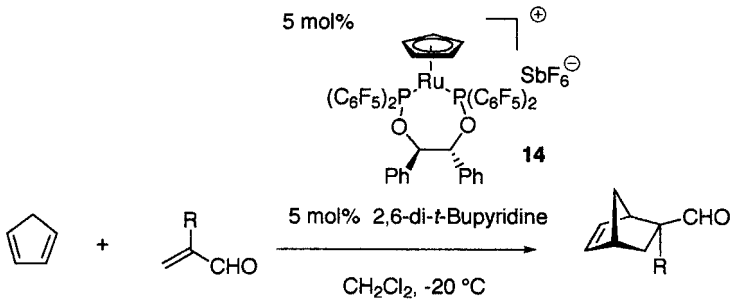
Scheme 1.26

Table 1.10 Asymmetric Diels-Alder reactions of cyclopentadiene catalyzed by **13** [19]

R^1	R^2	Temp. (°C)	Time (h)	Yield (%)	endo/exo	ee (%)
H	H	–30	16	44	62:38	87
H	Me	–20	20	83	2:98	97
H	Br	–20	2	83	6:94	95

1.2.1.5 **Ruthenium**

Kündig et al. recently applied the same perfluoroaryldiphosphonite ligand to the preparation of a cationic Ru catalyst **14** [20] (Scheme 1.27, Table 1.11). This catalyst also promotes the Diels-Alder reaction of α-bromoacrolein and cyclopentadiene, although this Diels-Alder reaction is slower than that catalyzed by the analogous cationic Fe complex **13**, and gives the cycloadducts with lower enantioselectivity (Fe 97% ee, Ru 92% ee).



Scheme 1.27

Table 1.11 Asymmetric Diels-Alder reactions of cyclopentadiene catalyzed by **14** [20]

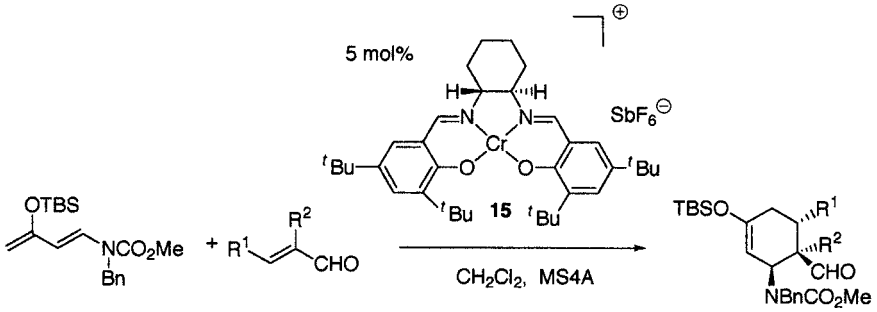
R	*Time (h)*	*Yield (%)*	*endo/exo*	*ee (%)*
Br	2	93	7:93	92
Me	22	91	3:97	92

1.2.1.6 **Chromium**

In most of the successful Diels-Alder reactions reported, dienes containing no heteroatom have been employed, and enantioselective Diels-Alder reactions of multiply heteroatom-substituted dienes, e.g. Danishefsky's diene, are rare, despite their tremendous potential usefulness in complex molecular synthesis. Rawal and coworkers have reported that the Cr(III)-salen complex **15** is a suitable catalyst for the reaction of α-substituted a,β-unsubstituted aldehydes with 1-amino-3-siloxy dienes [21] (Scheme 1.28, Table 1.12). The counter-ion of the catalyst is important and good results are obtained in the reaction using the catalyst paired with the SbF_6^- anion.

1.2.1.7 **Copper**

Kanemasa et al. discovered an asymmetric Diels-Alder reaction of acryloyl-oxazolidinone and cyclopentadiene catalyzed by a chiral aqua complex of 4,6-dibenzofuranidyl-2,2′-bis(4-phenyloxazoline) **16** (vide infra) [22]. Unlike the Diels-Alder reaction of acryloyloxazolidinone, for which $NiBr_2/AgClO_4$ and $ZnI_2/AgClO_4$ are the most suitable sources of the central metal, the best for the Diels-Alder reaction of α-bromo-



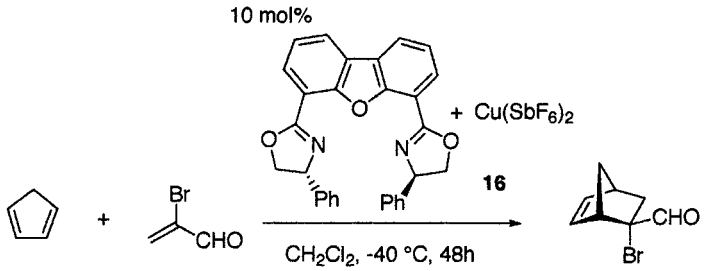
Scheme 1.28

Table 1.12 Asymmetric Diels-Alder reactions catalyzed by the Cr-salen complex **15** [21]

R^1	R^2	Temp. (°C)	Time (days)	Yield (%)	ee (%)
H	Me	–40	2	93	97
H	*i-Pr*	–40	5	92	>97
H	TBSO	–40	2	86	>97
–$(CH_2)_3$–		–40–23	5	76	96

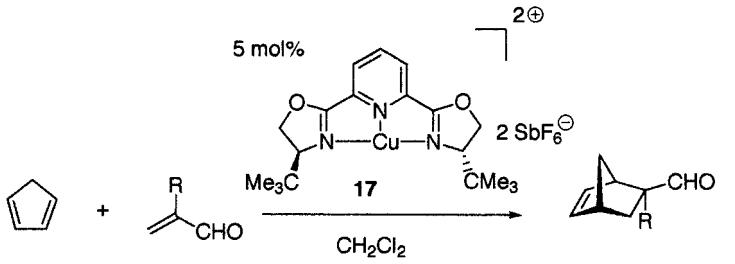
DiopBooks

acrolein and cyclopentadiene is $Cu(SbF_6)_2$, the catalyst derived from which gives the cycloadduct in 86% ee (Scheme 1.29). As only one example of the Diels-Alder reaction using *α,β*-unsaturated aldehydes has been reported, it is necessary to examine further the scope and limitations of the use of this catalyst with other aldehydes.



Scheme 1.29 86% ee, 93% , *endo:exo* = 3:97

Evans et al. reported that the bis(oxazolinyl)pyridine (pybox) complex of copper(II) **17** is a selective catalyst of Diels-Alder reactions between *α*-bromoacrolein or methacrolein and cyclopentadiene affording the adducts in high enantioselectivity [23] (Scheme 1.30). Selection of the counter-ion is important to achieve a satisfactory reaction rate and enantioselectivity, and $[Cu(pybox)](SbF_6)_2$ gave the best result. This catalyst is also effective for the Diels-Alder reaction of acrylate dienophiles (vide infra).



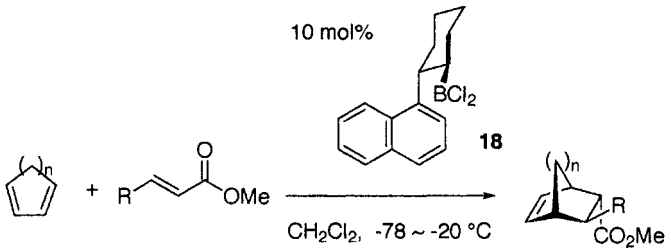
R = Me: -40°C, 8h, 92% ee, >95% convertion, *endo:exo* = 3:97
R = Br: -78°C, 12h, 96% ee, >95% convertion, *endo:exo* = 2:98

Scheme 1.30

1.2.2

The Asymmetric Diels-Alder Reaction of *α,β*-Unsaturated Esters as Dienophiles

Unlike many excellent results for the Diels-Alder reaction of *a,β*-unsaturated aldehydes (Section 2.1), and 3-alkenoyl-1,3-oxazolidin-2-ones (Section 2.3), there are few successful Diels-Alder reactions using *a,β*-unsaturated esters as the dienophile. Even so three outstanding asymmetric catalysts are described in this section. Hawkins et al. developed a chiral borane catalyst **18**, which was prepared by hydroboration of 1-(1-naphthyl)cyclohexene with $HBCl_2$, resolution with menthone, and then treatment with BCl_3 [24]. X-ray structural analysis of the complex of the catalyst and methyl crotonate revealed not only the usual binding of the carbonyl to the Lewis acid but also additional binding – an electrostatic and dipole-induced dipole attraction between the boron-activated carboalkoxy group of the dienophile and the electron-rich and polarizable arene of the catalyst. In the presence of this catalyst cyclopentadiene and cyclohexadiene react with methyl acrylate, methyl crotonate, and dimethyl fumarate to afford the adducts in high optical purity (Scheme 1.31, Table 1.13).



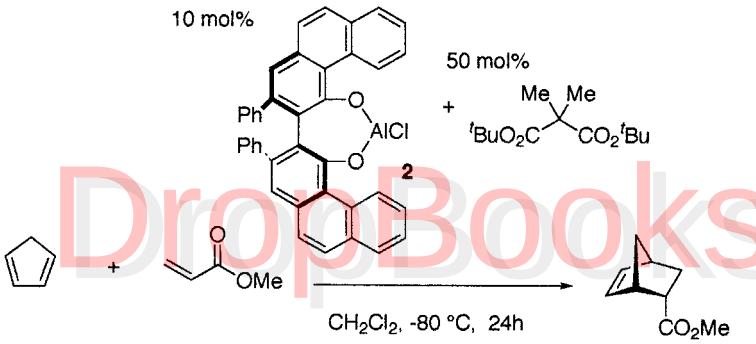
Scheme 1.31

Wulff and coworkers have applied their aluminum catalyst **2** containing a vaulted biphenanthrol ligand (VAPOL, Section 2.1) to the Diels-Alder reaction between methyl acrylate and cyclopentadiene [25] (Scheme 1.32). In this Diels-Alder reaction auto-induction is observed, because of a cooperative interaction between the product

Table 1.13 Asymmetric Diels-Alder reactions catalyzed by **18** [24]

R	*n*	*Yield (%)*	*ee (%)*
H	1	97	97
Me	1	91	93
CO_2Me	1	92	90
H	2	83	86

with the catalyst to generate a new, more selective catalyst species. In the presence of di-*tert*-butyl dimethylmalonate (50 mol%), the optical purity of the product was increased from 82% ee to >99% ee. This additive mimics the auto-inductive effect of the product but achieves greater inductions than are possible with product alone.



Scheme 1.32

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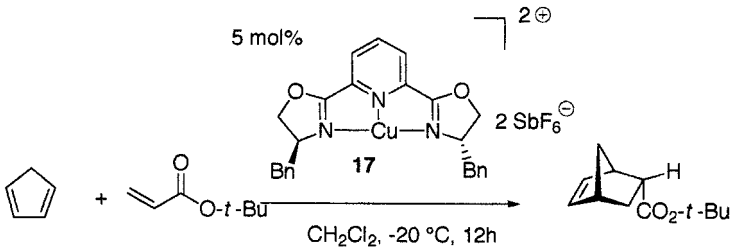
Evans's bis(oxazolinyl)pyridine (pybox) complex **17**, which is effective for the Diels-Alder reaction of α-bromoacrolein and methacrolein (Section 2.1), is also a suitable catalyst for the Diels-Alder reaction of acrylate dienophiles [23] (Scheme 1.33). In the presence of 5 mol% of the Cu((*R*)-pybox)$(SbF_6)_2$ catalyst with a benzyl substituent, *tert*-butyl acrylate reacts with cyclopentadiene to give the adduct in good optical purity (92% ee). Methyl acrylate and phenyl acrylate underwent cycloadditions with lower selectivities.

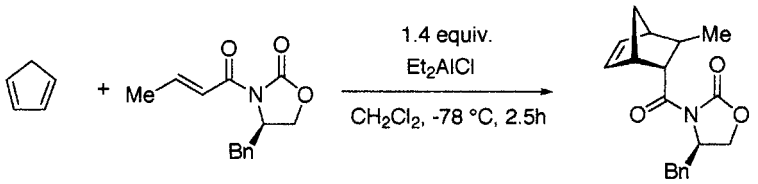
1.2.3
The Asymmetric Diels-Alder Reaction of 3-Alkenoyl-1,3-oxazolidin-2-ones as Dienophile

Chiral 3-alkenoyl-1,3-oxazolidin-2-ones have been developed and used in highly diastereoselective Diels-Alder reactions by Evans et al. [26] (Scheme 1.34). In this reaction these dienophiles are highly reactive compared with the corresponding



Scheme 1.33 92% ee, 93% , *endo*:*exo* = 98:2

ester. Lewis acids such as Et_2AlCl coordinate to the dienophile in a two-point binding fashion (Fig. 1.5). After Evans's investigations of the diastereoselective reactions of chiral 3-alkenoyl-1,3-oxazolidin-2-ones, many chiral Lewis acids have been developed and applied to the Diels-Alder reaction of their achiral 3-alkenoyl-1,3-oxazolidin-2-one counterparts.



Scheme 1.34

The first successful application of a chiral Lewis acid to the Diels-Alder reaction of these 3-alkenoyl-1,3-oxazolidin-2-ones was Narasaka's TADDOL-based, chiral titanium catalyst in 1986 (vide infra) [27]. A catalytic amount of this chiral titanium reagent can promote the Diels-Alder reaction highly efficiently to give the cycloadduct in over 90% ee. Since Narasaka's work the Diels-Alder reaction of 3-alkenoyl-1,3-oxazolidin-2-ones has come to be regarded as a test case for newly-developed chiral Lewis acids having two-point binding ability, because the cycloadducts obtained are synthetically useful chiral building blocks. Complexes derived from many kinds of metal, including Al(III), Mg(II), Cu(II), Fe(III), Ni(II), Ti(IV), Zr(IV), and Yb(III) with chiral ligands have been devised. In this section the catalysts are classified according to their central metal.

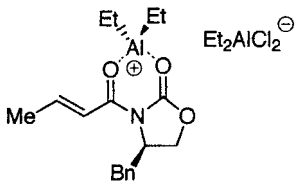
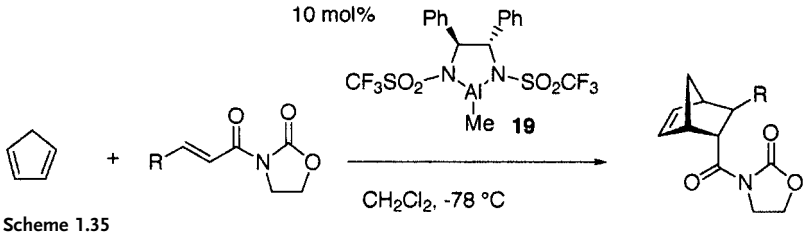


Fig. 1.5 Coordination of Et_2AlCl with chiral crotonoyl-1,3-oxazolidin-2-one derivative

1.2.3.1 Aluminum

Corey et al. reported that the catalyst **19**, prepared from trimethylaluminum and the bis-trifluorosulfonamide of stilbenediamine (stien), with generation of methane, is a suitable catalyst for the Diels-Alder reaction of 3-acryloyl, and 3-crotonoyl-1,3-oxazolidin-2-ones, giving the cycloadducts in high optical purity [28] (Scheme 1.35, Table 1.14). X-ray structure analysis of the catalyst and ^{1}H and ^{13}C NMR studies revealed that 3-alkenoyl-1,3-oxazolidin-2-one binds with the chiral Lewis acid at a single point, though the dienophile is thought to be a good two-point binding ligand [29]. The dienophile is, moreover, thought to adopt an *s-trans* conformation in the transition state, while the reaction proceeds through the *s-cis* conformation for other chiral Lewis acids. This catalyst has also been applied to the Diels-Alder reaction of 5-(benzoxymethyl)-1,3-cyclopentadiene in the synthesis of a key intermediate for prostaglandins.



Scheme 1.35

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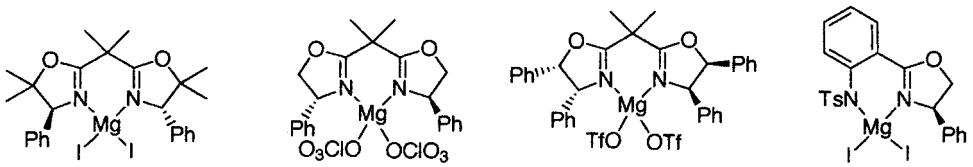
Table 1.14 Asymmetric Diels-Alder reactions catalyzed by **19** [28]

R	*Yield (%)*	*endo/exo*	*ee (%)*
H	92	>50:1	91
Me	88	96:4	94

1.2.3.2 Magnesium

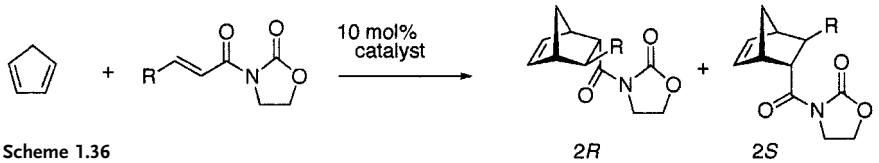
Several chiral magnesium catalysts have been reported. Corey et al. found that bis(oxazoline)magnesium catalyst **20** promotes the Diels-Alder reaction of acryloyl oxazolidinone and cyclopentadiene to give adducts in 91% ee [30]. The catalyst **20** was prepared from bis(oxazoline) and magnesium iodide in the presence of I_2 to remove iodide. Other bis(oxazoline)-magnesium catalysts have been intensively investigated by Desimoni et al. [31], who prepared them from three different bis(oxazolines) and magnesium perchlorate or triflate. Although the catalyst **21**, with the perchlorate anion, gave the 2*S* adduct in moderate optical purity (72% ee) on reaction of acryloyl derivative and cyclopentadiene, the opposite enantiomer (2*R*, 70% ee) was obtained by adding 2 equiv. water under the same reaction conditions. This is one of the few examples where the absolute stereochemistry of the product is reversed by an achiral additive. The best optical purity was realized by the catalyst **22** containing the triflate anion, which gave the cycloadduct in 93%



20 **21** **22** **23**

Fig. 1.6 Chiral magnesium catalysts

ee. Another chiral ligand, this one containing both mono-oxazoline and sulfonylamino groups, was developed by Fujisawa [32]. The magnesium complex **23** of this ligand promotes the Diels-Alder reaction with good enantioselectivity, though the necessary catalyst loading is 50 mol%. Representative results for the reaction in Scheme 1.36 catalyzed by 20–23 are presented in Table 1.15.



Scheme 1.36 *2R* *2S*

Table 1.15 Asymmetric Diels-Alder reactions of cyclopentadiene catalyzed by **20**–**23** [30–32]

Catalyst	*R*	*Temp. (°C)*	*Time (h)*	*Yield (%)*	*endo/exo*	*ee (%)*
20	H	–80	24	82	97:3	90.6 (2*R*)
21	H	–50	12	Quant.	92:8	72 (2*S*)
21 + H_2O	H	–50	12	Quant.	93:7	70 (2*R*)
22	H	–50	12	Quant.	94:6	93 (2*R*)
22	Me	–15	48	97	84:16	92 (2*R*)
23 (50 mol%)	H	–78	2	81	–	91 (2*R*)

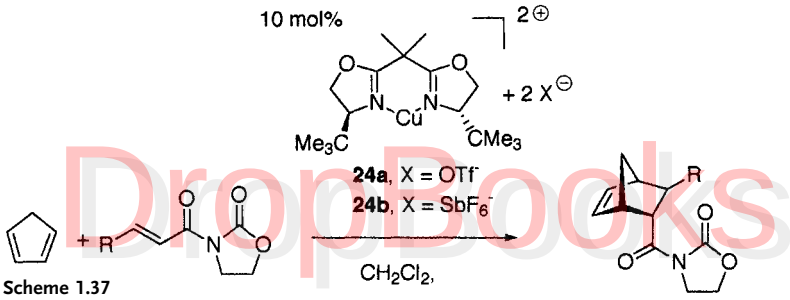
1.2.3.3 **Copper**

Evans et al. have found that the C_2-symmetric bis(oxazoline)-derived Cu(II) complexes **24** are highly enantioselective catalysts of the Diels-Alder reaction of 3-alkenoyl-1,3-oxazolidin-2-ones [23, 33] (Scheme 1.37, Table 1.16). After tuning the ligand of the catalyst, it was discovered that the bis(oxazoline) ligand derived from *tert*-leucine is effective when $Cu(OTf)_2$ is used as the metal source. $Cu(OTf)_2$ is superior both in chemical and optical yields to the other metal triflates examined – AgOTf, $Zn(OTf)_2$, $Cd(OTf)_2$, $Co(OTf)_2$, $Mn(OTf)_2$, $Lu(OT)_3$, $Sm(OTf)_3$, LiOTf, and $Ni(OTf)_2$ [33a,b]. The effect of the catalyst counter-ions was investigated, revealing its profound influence on both the reaction rate and stereoselectivity. Of the counter-ions examined (SbF_6^-, PF_6^-, BF_4^-, and OTf^-), the catalyst with the SbF_6^- counter-ion had the highest enantioselectivity and Lewis acidity, and afforded the cycloadduct in very high optical purity

in a short reaction time at low temperature [33a,c]. Another noteworthy feature of the catalyst **24b** is its exceptional temperature profile. The enantiomeric excess of the Diels-Alder product of acryloyloxazolidinone and cyclopentadiene is not greatly affected by reaction temperature (>98% ee at –78 °C, 94% ee at 25 °C).

With few exceptions chiral Lewis acids are usually moisture-sensitive and require anhydrous conditions, but bench-stable aquo complexes such as [Cu(*S*,*S*)-*t*-Bu-box)$(H_2O)_2$]$(SbF_6)_2$ were found to promote the Diels-Alder reaction as effectively as the anhydrous copper reagent.

The reaction has wide scope in respect of the dienophile *β*-substituent. The representative less reactive dienophiles, crotonoyl- and cinnamoyl-oxazolidinone, react with cyclopentadiene at –15 °C and 25 °C for 20 h and 24 h giving cycloadducts in 99% ee and 96% ee, respectively. The 3-chloropropenoyl derivative also affords the adduct in high optical purity (96% ee); this adduct is transformed to 2-(methoxycarbonyl)norbornadiene, a useful chiral building block. Thus, the 3-chloropropenoyl derivative can be regarded as a synthetic equivalent of an acetylene dienophile.



Scheme 1.37

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Table 1.16 Asymmetric Diels-Alder reactions of cyclopentadiene catalyzed by **24** [33 a]

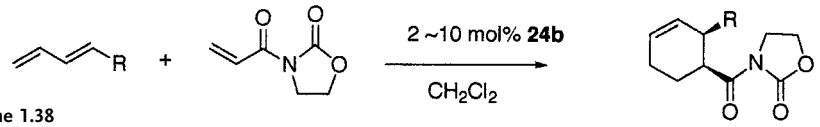
Catalyst	*R*	*Temp. (°C)*	*Time (h)*	*Yield (%)*	*endo/exo*	*ee (%)*
24a	H	–78	10	a*	98:2	>98
24b	H	–78	4	a*	96:4	>98
24b	H	25	10 min	a*	86:14	94
24b	Me	–15	20	99	85:15	99
24b	Ph	–10	48	77	88:12	98
24a	CO_2Et	–55	20	92	94:6	95
24b	Cl	25	24	96	87:13	96

* 100% conversion

Less reactive dienes such as cyclohexadiene can be employed efficiently, giving the adduct in 90% yield in 93% ee. Acyclic dienes such as piperylene, 2,4-hexadiene, and 1-phenylbutadiene also react with the acryloyloxazolidinone derivative to afford Diels-Alder cycloadducts in high optical yields (Scheme 1.38, Table 1.17).

Compared with these dienes, a decrease in enantioselectivity was observed in those unsubstituted at the 1-position; isoprene and 2,3-dimethylbutadiene gave the products in only 59% ee and 65% ee, respectively.

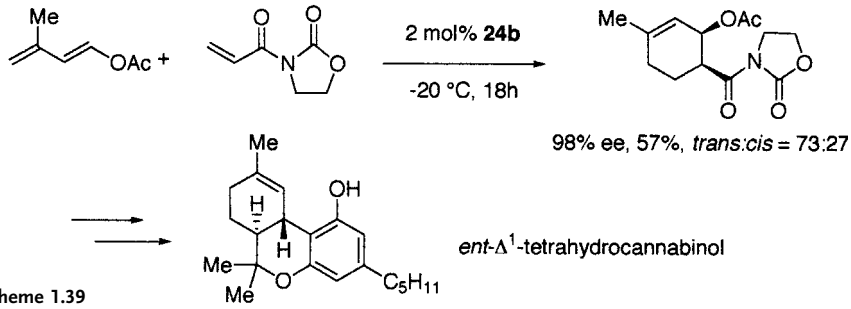
A great advantage of catalyst **24b** compared with other chiral Lewis acids is that it tolerates the presence of ester, amine, and thioether functionalities. Dienes substituted at the 1-position by alkyl, aryl, oxygen, nitrogen, or sulfur all participate effectively in the present asymmetric Diels-Alder reaction, giving adducts in over 90% ee. The reaction of 1-acetoxy-3-methylbutadiene and acryloyloxazolidinone catalyzed by copper reagent **24b**, affords the cycloadduct in 98% ee. The first total synthesis of *ent*-Δ^1-tetrahydrocannabinol was achieved using the functionalized cycloadduct obtained [23, 33e] (Scheme 1.39).



Scheme 1.38

Table 1.17 Asymmetric Diels-Alder reactions of acryloyloxazolidinone catalyzed by **24b** [23]

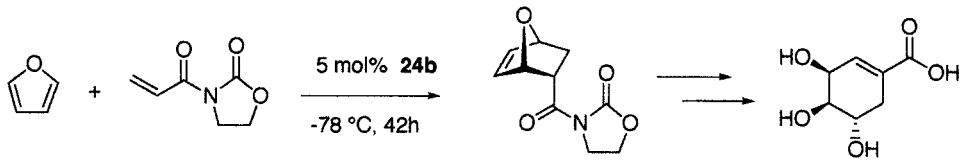
R	*Temp. (°C)*	*Time (h)*	*Yield (%)*	*cis/trans*	*ee (%)*
Me	25	12	89	83:17	94
Ph	–20	24	95	85:15	97
OAc	0	24	75	85:15	96
SPh	–20	24	84	98:2	98
NHCbz	0	24	54	72:28	90



Scheme 1.39

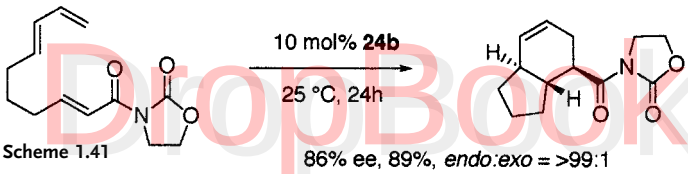
Although furan is usually a poor diene in the Diels-Alder reaction, the chiral copper reagent **24b** promotes its asymmetric addition to acryloyloxazolidinone to afford the 7-oxabicyclo[2.2.1]hept-2-ene derivative in high optical purity (Scheme 1.40). Because a retro-Diels-Alder reaction occurs above –20 °C, the reaction must be performed at low temperature (–78 °C) to obtain a high optical yield. The bicy-

clo compound obtained, which was recrystallized to optically pure, was successfully converted to *ent*-shikimic acid in a few steps [23, 33f].



Scheme 1.40 97%ee, 97% conversion, *endo:exo*=80:20 *ent*-shikimic acid

The chiral copper reagent **24** is an effective catalyst not only for intermolecular, but also for intramolecular Diels-Alder reactions, as shown in the following schemes (Scheme 1.41, 1,42, 1.43). Synthetically useful octalin and decalin skeletons were synthesized in high enantio- and diastereoselectivity. The synthetic utility of this intramolecular Diels-Alder reaction has been demonstrated by a short total synthesis of isopulo'upone [23, 33d].



Scheme 1.41 86% ee, 89%, *endo:exo* = >99:1

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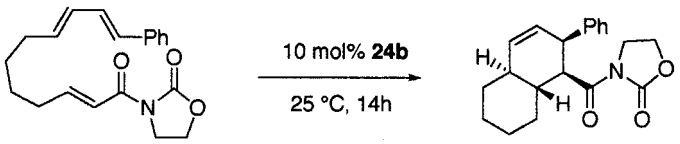
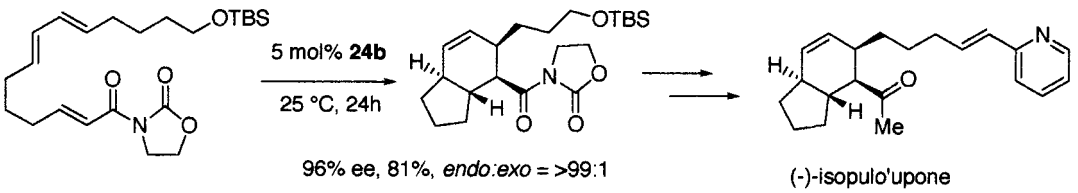


Scheme 1.42 97% ee, 97%, *endo:exo* = 84:16



96% ee, 81%, *endo:exo* = >99:1 (-)-isopulo'upone

Scheme 1.43

A transition state structure for [Cu((*S*,*S*)-*tert*-Bu-box)$(H_2O)_2$]X_2 (X = OTf or SbF_6) and dienophile has been proposed on the basis of X-ray structures of complexes such as [Cu((*S*,*S*)-*tert*-Bu-box)$(H_2O)_2$]X_2 (X = OTf and SbF_6) and [Cu((*S*,*S*)-*tert*-Bu-

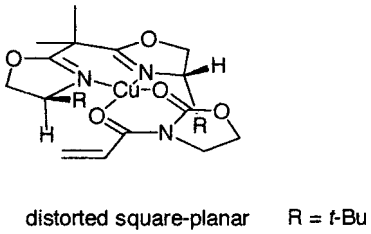
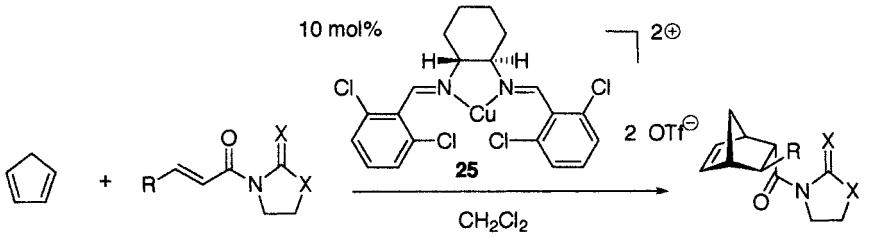


Fig. 1.7 Coordination of **24** to acryloyloxazolidinone

box)]Cl_2, and a PM3 calculation on the [Cu((*S*,*S*)-*tert*-Bu-box)(acrylimide)]$^{2+}$ complex. The dienophile, which adopts the *s-cis* conformation, is bound to the catalyst in the plane of the ligand in a bidentate manner. Solution-phase EPR data shows the complex to have distorted four-coordinate square-planar geometry. According to this model, the *tert*-butyl group shields the top face and cycloaddition proceeds from the bottom [23] (Fig. 1.7).

Evans et al. reported that the bis(imine)-copper (II) complex **25**, prepared from chiral bis(imine) ligand and $Cu(OTf)_2$, is also an effective chiral Lewis acid catalyst [34] (Scheme 1.44, Table 1.18). By tuning the aryl imine moiety, the bis(2,6-dichlorophenylimine) derivative was found to be suitable. Although the *endo*/*exo* selectivity for 3-alkenoyloxazolidinones is low, significant improvement is achieved with the thiazolidine-2-thione analogs, for which both dienophile reactivity and *endo*/*exo* selectivity are enhanced.

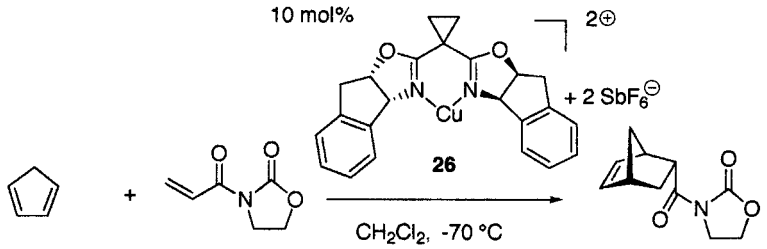


Scheme 1.44

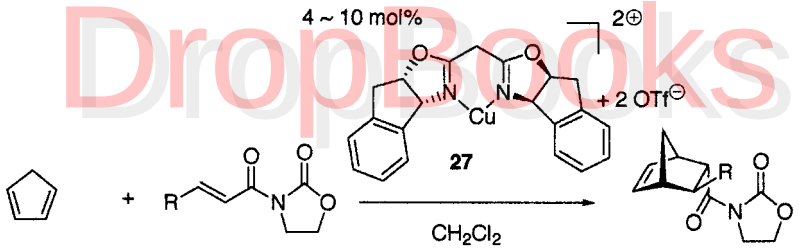
Table 1.18 Asymmetric Diels-Alder reactions of cyclopentadiene catalyzed by **25** [34]

R	*X*	*Temp. (°C)*	*Time (h)*	*Yield (%)*	*endo/exo*	*ee (%)*
H	O	–78	30	87	80:20	92
Me	O	–10	30	90	65:35	83
Me	S	–30	16	86	93:7	91
Ph	O	25	84	83	60:40	85
Ph	S	–20	48	84	92:8	92
CO_2Et	O	–55	24	98	55:45	94
CO_2Et	S	–55	24	99	90:10	88

Since Evans's initial report, several chiral Lewis acids with copper as the central metal have been reported. Davies et al. and Ghosh et al. independently developed a bis(oxazoline) ligand prepared from aminoindanol, and applied the copper complex of this ligand to the asymmetric Diels-Alder reaction. Davies varied the link between the two oxazolines and found that cyclopropyl is the best connector (see catalyst **26**), giving the cycloadduct of acryloyloxazolidinone and cyclopentadiene in high optical purity (98.4% ee) [35] (Scheme 1.45). Ghosh et al., on the other hand, obtained the same cycloadduct in 99% ee by the use of unsubstituted ligand (see catalyst **27**) [36] (Scheme 1.46, Table 1.19).



Scheme 1.45 98.4%ee, *endo*:*exo*=59:1



Scheme 1.46

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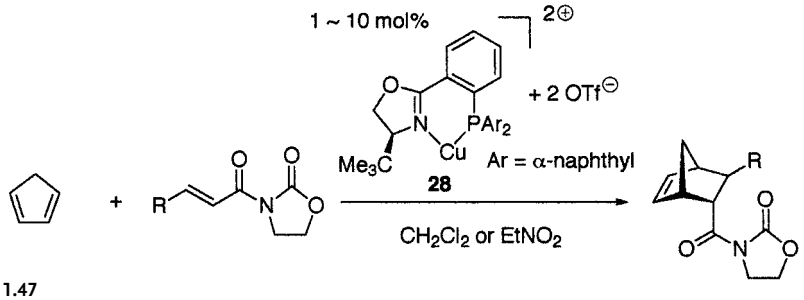
Table 1.19 Asymmetric Diels-Alder reactions of cyclopentadiene catalyzed by **27** [36]

R	*Temp. (°C)*	*Time (h)*	*Yield (%)*	*trans/cis*	*ee (%)*
H	–78	8	90	>99:1	99
Me	0	48	77	90:10	84
Ph	23	72	78	80:20	35
CO_2Et	–45	8	75	93:7	94

(Phosphino-oxazoline)copper complex **28** was found by Helmchen et al. to be an excellent Diels-Alder catalyst [37] (Scheme 1.47, Table 1.20). The nitrogen atom acts as an electron-donating ligand, whereas phosphorus is a σ-donor-π-acceptor ligand. The copper complex of this phosphino-oxazoline ligand is therefore expected to have

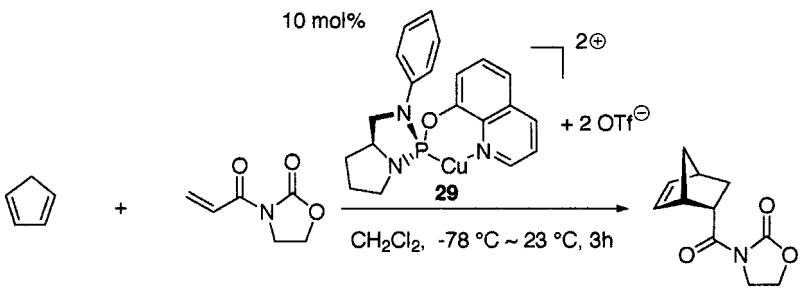
higher Lewis acidity than that of bis(oxazolidine) ligands. In fact, acryloyl-, crotonoyl-, cinnamoyl-, and fumaroyl-oxazolidinones react with cyclopentadiene to give the cycloadducts in 97%, 86%, 85% and 75% ee, respectively. Dichloromethane and nitromethane are both suitable solvents. As little as 1 mol% catalyst **28** is enough to bring the reaction of the acryloyl derivative and cyclopentadiene to completion, giving the cycloadduct in 92% ee. An interesting observation is that the *exo* isomer is formed predominantly from the cinnamoyl derivative, in contrast with the other dienophiles for which the *endo* isomer is the major. The copper reagent having the triflate counter-ion gave a better result than that with the SbF_6^- anion.



Scheme 1.47

Table 1.20 Asymmetric Diels-Alder reactions of cyclopentadiene catalyzed by **28** [37]

R	*Temp. (°C)*	*Time (h)*	*Yield (%)*	*trans/cis*	*ee (%)*
H	–78	2.5	92	94:6	97
Me	–20	42	98	88:12	86
Ph	23	64	74	40:60	85 (*exo*), 32 (*endo*)
CO_2Et	–40	4	95	60:40	75



Scheme 1.48

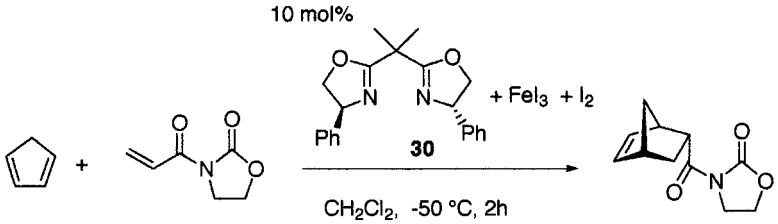
>99%ee, >99% conversion, *endo*:*exo*=>98:2

A quinoline-phosphine ligand has been developed by Buono et al., and its complex **29** with $Cu(OTf)_2$ found to be an effective catalyst for the Diels-Alder reaction between acryloyl-oxazolidinone and cyclopentadiene, affording the cycloadduct

with complete enantioselectivity (>99% ee) [38] (Scheme 1.48). Further studies are needed to investigate the scope and limitations of this chiral catalyst.

1.2.3.4 Iron

Corey et al. synthesized a chiral bis(oxazoline)Fe(III) catalyst **30**, the ligand of which was prepared from chiral phenylglycine. The catalyst was formed by the reaction of the ligand with FeI_3 in the presence of I_2. I_2 greatly enhances the Lewis acidity of the catalyst owing to the formation of a cationic species [39] (Scheme 1.49).



Scheme 1.49 95%, 82% ee, *endo:exo* = 96:4

1.2.3.5 Nickel

The *trans*-chelating tridentate ligand, 4,6-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline) (abbreviated to DBFOX), is an effective source of chirality for the Diels-Alder reaction when complexed with a variety of transition-metal(II) perchlorates [22] (Scheme 1.50, 1.51, Table 1.21). $Fe(ClO_4)_2$, $Co(ClO_4)_2$, $Ni(ClO_4)_2$, $Cu(ClO_4)_2$, and $Zn(ClO_4)_2$ can all be employed as the source of the central metal of the Lewis acid, and use of any of them gives high enantioselectivity. The wide applicability of this ligand toward so many metals is remarkable, although of the above metals, nickel was found to be most efficient. Although coordination of the three electronegative ligands to a metallic center would be expected to reduce the Lewis acidity, the employment of a non-coordinating counter-ion can, conversely, increase it. The catalysts are stable to moisture, and the aqua complexes work equally well as

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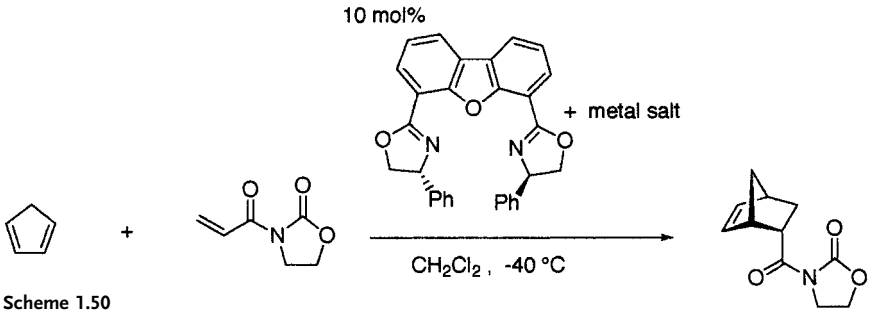
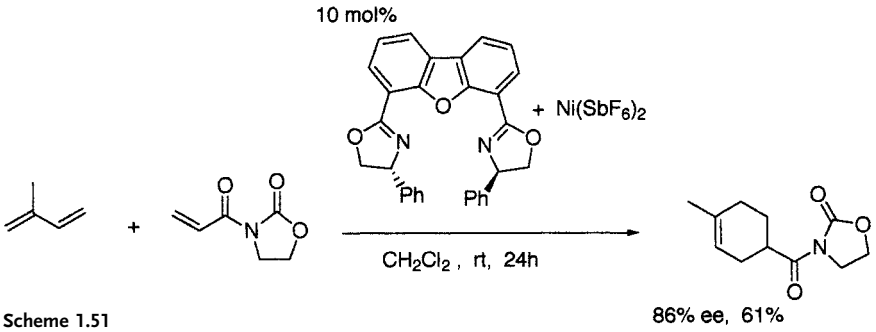


Scheme 1.50

catalysts, which is a great synthetic advantage. Not only the acryloyl derivative, but also the crotonoyl and cinnamoyl imides react with cyclopentadiene, giving adducts of high optical purity.

Table 1.21 Effect of metal salt on enantioselectivity in the Diels-Alder reaction of cyclopentadiene and acryloyloxazolidinone [22]

Metal salt	*Time (h)*	*Yield (%)*	*endo/exo*	*ee (%)*
$Ni(ClO_4)_2$	24	Quant	95:5	96
$Ni(ClO_4)_2 \cdot 6H_2O$	14	96	97:3	>99
$Mn(ClO_4)_2 \cdot 6H_2O$	96	96	97:3	83
$Fe(ClO_4)_2$	48	90	99:1	98
$CO(ClO_4)_2 \cdot 6H_2O$	48	97	97:3	99
$Cu(ClO_4)_2$	48	97	96:4	92
$Cu(ClO_4)_2 + 3H_20$	15	99	97:3	96
$Zn(ClO_4)_2$	48	99	98:2	97



Scheme 1.51

A transition-state structure was proposed on the basis of the solid-state structure of $[Ni((R,R)\text{-DBFOX})(H_2O)_3](ClO_4)_2$ (Fig. 1.8). The catalyst–dienophile complex is thought to be a square-bipyramidal structure containing an octahedral nickel ion. The dienophile adopts an *s-cis* conformation with the *si* face shielded by a phenyl group.

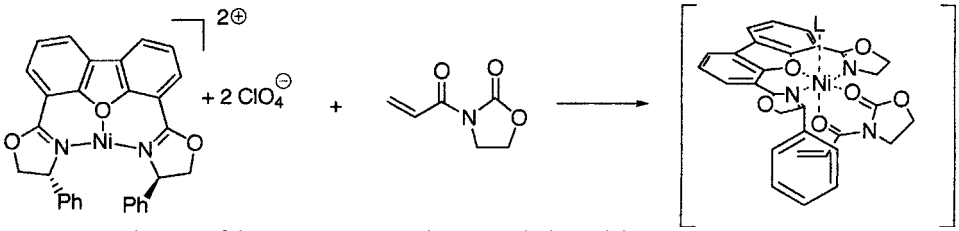


Fig. 1.8 Coordination of the DBFoX-Ni(II) catalyst to acryloyloxazolidinone

1.2.3.6 **Titanium**

The first practical Diels-Alder catalyst for 3-alkenoyloxazolidinones was Narasaka's TADDOL-based, chiral titanium catalyst **31** reported in 1986 [27, 40], as described at the beginning of this section (Scheme 1.52). Tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) ligands were easily prepared from tartaric acid [41]. The most effective TADDOL in the current Diels-Alder reaction is one with the 1-phenylethylidene group as the acetal center. The chiral catalyst **31** was formed simply by mixing dichlorodiisopropoxytitanium and TADDOL. Although the use of a catalytic amount of the titanium reagent **31** alone did not give reproducible asymmetric induction, it was discovered that the combined use of 4-Å molecular sieves (MS 4 Å) with a catalytic amount (10 mol%) of the chiral titanium reagent afforded the Diels-Alder adducts with good to high (61–91% ee), reproducible, enantioselectivity.

Another issue important to the success of this chiral titanium reagent **31** was the discovery of a marked solvent effect. When the fumaric acid derivative is reacted with isoprene in the presence of 10 mol% of the titanium reagent **31** in toluene, poor optical purity results (36–68% ee). Interestingly the optical purity of the adduct greatly increased in the order benzene, toluene, xylenes, and mesitylene, with 92% ee obtained in the last. Mesitylene is difficult to remove, because of its high boiling point, and other solvents were screened in detail. As a result, the mixed solvent system toluene petroleum ether (1:1) was discovered to be very effective.

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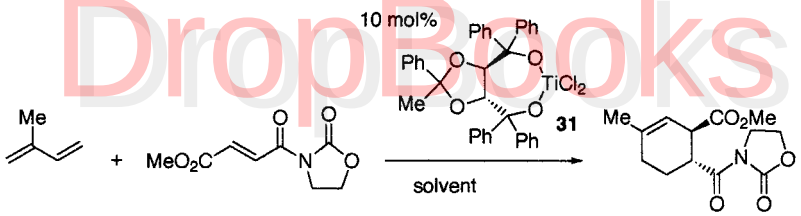


benzene 41% ee, toluene 36-68% ee, mesitylene 93% ee, $CFCl_3$ 92% ee, Et_2O 91% ee
toluene-P.E. 94% ee

Scheme 1.52

The Diels-Alder reaction catalyzed by this chiral titanium catalyst **31** has wide generality (Scheme 1.53, 1.54, Table 1.22, 1.23). Acryloyl- and fumaroyl-oxazolidinones react with isoprene giving cycloadducts in high optical purity. 2-Ethylthio-1,3-butadiene can also be successfully employed as the diene [42].

For the construction of oxygen-functionalized Diels-Alder products, Narasaka and coworkers employed the 3-borylpropenoic acid derivative in place of 3-(3-acetoxypropenoyl)oxazolidinone, which is a poor dienophile in the chiral titanium-catalyzed reaction (Scheme 1.55, Table 1.24). 3-(3-Borylpropenoyl)oxazolidinones react smoothly with acyclic dienes to give the cycloadducts in high optical purity [43]. The boryl group was converted to an hydroxyl group stereospecifically by oxidation, and the alcohol obtained was used as the key intermediate in a total synthesis of (+)-paniculide A [44] (Scheme 1.56).

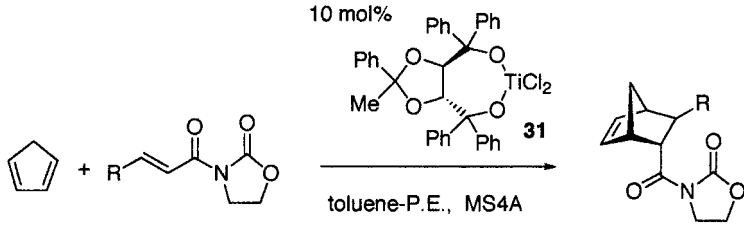
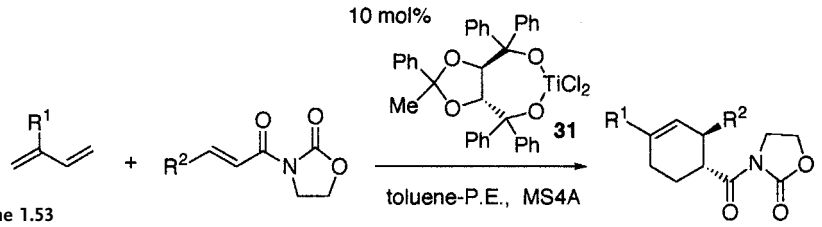


Table 1.22 Asymmetric Diels-Alder reactions of cyclopentadiene catalyzed by **31** [40b, 42]

R	*Yield (%)*	*endo/exo*	*ee (%)*
H	81	>95:5	88
Me	91	87:13	94
Ph	76	92:8	80
Pr	72	91:9	75



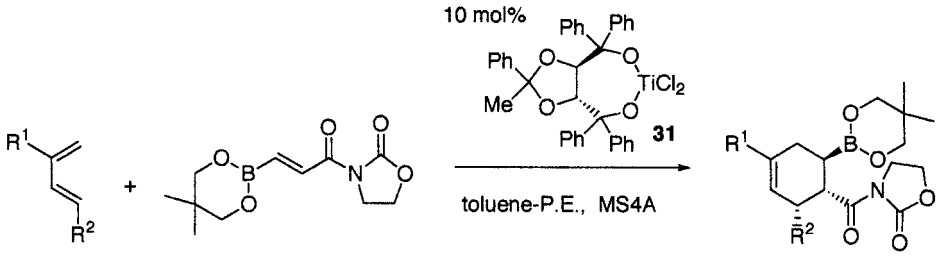
Scheme 1.53

Table 1.23 Asymmetric Diels-Alder reactions of a variety of dienes catalyzed by **31** [40b, 42]

R^1	R^2	*Yield (%)*	*ee (%)*
H	COOMe	84	91
Me	COOMe	94	94
H	H	81	93[a]
Me	H	93	>96[a]
SEt	H	72	91

[a] A mixture of *p*-xylene-P.E. (11) was used as a solvent

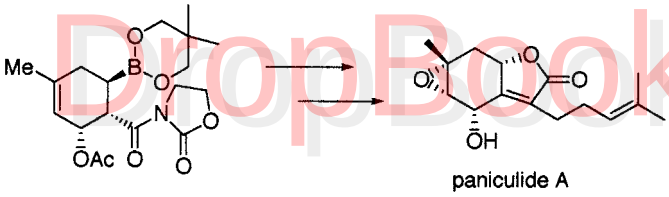
Application of this catalytic process was extended to asymmetric intramolecular Diels-Alder reactions. Synthetically useful intermediates with octalin and decalin skeletons were obtained in high optical purity by use of a catalytic amount of the chiral titanium reagent [45] (Scheme 1.57, Table 1.25). The core part of the mevinic acids was enantioselectively synthesized by use of this asymmetric intramolecular reaction [46] (Scheme 1.58).



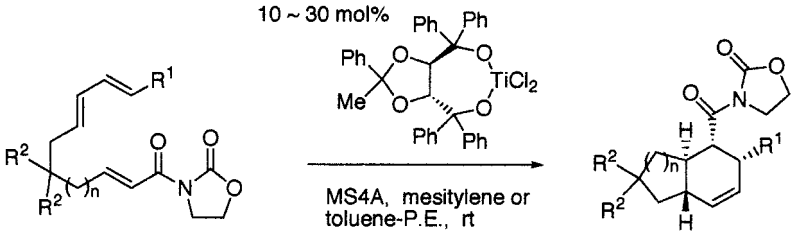
Scheme 1.54

Table 1.24 Asymmetric Diels-Alder reactions of 3-borylpropenoic acid derivatives catalyzed by **31** [43]

R^1	R^2	*Yield (%)*	*ee (%)*
H	H	76	>98
Me	H	74	>98
Me	Me	92	94
Me	OAc	71	95



Scheme 1.55



Scheme 1.56

Table 1.25 Asymmetric intramolecular Diels-Alder reactions catalyzed by **31** [45]

R^1	R^2	*n*	*Time (h)*	*Yield (%)*	*ee (%)*
H	H	1	257	87	87
H	SCH_2CH_2S	1	68	62	95
H	SCH_2CH_2S	2	120	64	86
Me	SCH_2CH_2S	2	120	70	87

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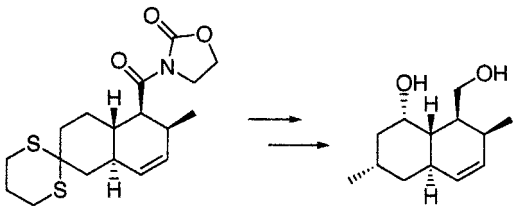
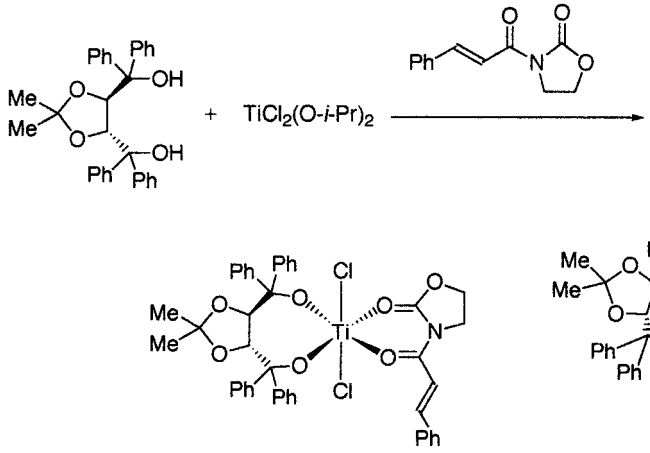


Scheme 1.57

The titanium catalyst **31** is prepared in-situ by mixing the chiral TADDOL and $TiCl_2(O\text{-}i\text{-}Pr)_2$ in toluene in the presence of MS 4 Å with the generation of isopropyl alcohol (Scheme 1.59). A ^1H NMR study showed that formation of the titanium reagent **31** was incomplete, and approximately 16% of the uncomplexed TADDOL remains. The observation of a lower chemical shift for the methine proton of isopropyl alcohol in the mixture, compared with that of isopropyl alcohol itself suggests that the coordination of isopropyl alcohol causes aggregation of the achiral titanium species ($TiCl_2(O\text{-}i\text{-}Pr)_2$) reducing its activity as a Lewis acid [47].

Scheme 1.58 **31**

A chiral titanium complex with 3-cinnamoyl-1,3-oxazolidin-2-one was isolated by Jørgensen et al. from a mixture of $TiCl_2(O\text{-}i\text{-}Pr)_2$ with (2*R*,3*R*)-2,3-*O*-isopropylidene-1,1,4,4-tetraphenyl-1,2,3,4-butanetetrol, which is an isopropylidene acetal analog of Narasaka's TADDOL [48]. The structure of this complex was determined by X-ray structure analysis. It has the isopropylidene diol and the cinnamoyloxazolidinone in the equatorial plane, with the two chloride ligands in apical (*trans*) position as depicted in the structure **A**. It seems from this structure that a pseudo-axial phenyl group of the chiral ligand seems to block one face of the coordinated cinnamoyloxazolidinone. On the other hand, after an NMR study of the complex in solution, Di Mare et al. and Seebach et al. reported that the above *trans* dichloro complex **A** is a major component in the solution but went on to propose another minor complex **B**, with the two chlorides *cis* to each other, as the most reactive intermediate in this chiral titanium-catalyzed reaction [41b, 49]. It has not yet been clearly confirmed whether or not the *trans* and/or the *cis* complex are real reactive intermediates (Scheme 1.60).



Scheme 1.59 **A** : *trans*-dichloro **B** : *cis*-dichloro

1.2.3.7 **Zirconium**

Collins and coworkers applied the bis(tetrahydroindenyl)zirconium triflate **32**, which is used as a polymerization catalyst, to the asymmetric Diels-Alder reaction [50] (Scheme 1.61). A remarkable solvent effect was observed – although only a low optical yield was obtained in CH_2Cl_2, high optical purity (91% ee) was realized in 2-nitropropane by use of only 1 mol% of the catalyst. The catalyst is also effective for crotonoyloxazolidinone, giving the cycloadduct in 90% ee.

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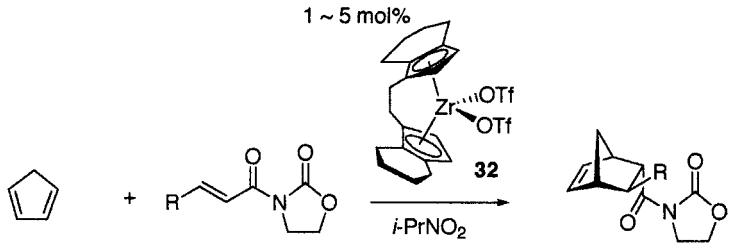


R = H, 91% ee, 83%, *endo*:*exo* = 11.5/1
R = Me, 90% ee, 87%, *endo*:*exo* = 5/1

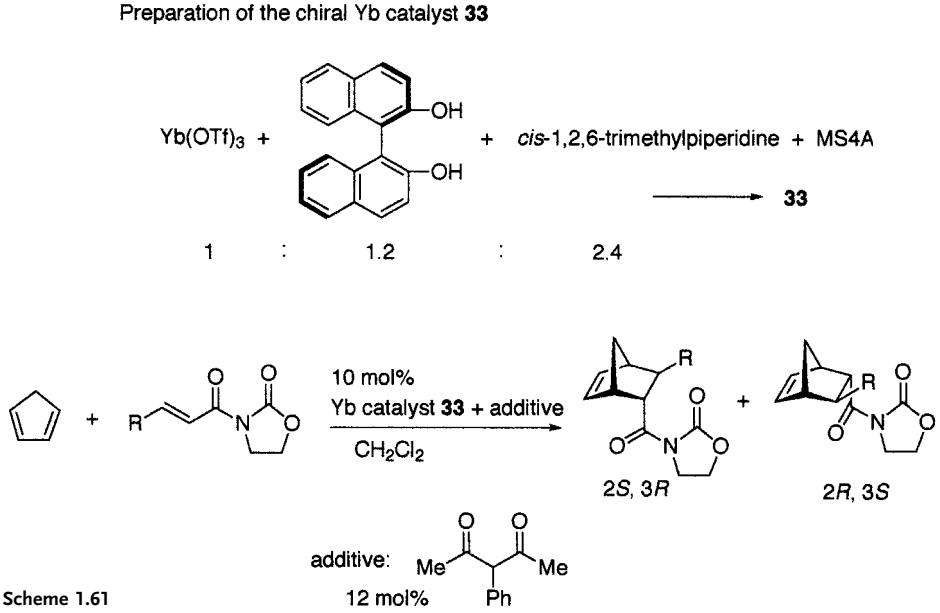
Scheme 1.60

1.2.3.8 **Lanthanides**

Kobayashi et al. have reported the use of a chiral lanthanide(III) catalyst for the Diels-Alder reaction [51] (Scheme 1.63, Table 1.26). Catalyst **33** was prepared from binaphthol, lanthanide triflate, and *cis*-1,2,6-trimethylpiperidine (Scheme 1.62). When the chiral catalyst prepared from ytterbium triflate ($Yb(OTf)_3$) and the lithium or sodium salt of binaphthol was used, less than 10% ee was obtained, so the amine exerts a great effect on the enantioselectivity. After extensive screening of amines, *cis*-1,2,6-

trimethylpiperidine was found to be the optimum base; when this was used the cycloadduct was obtained in 95% ee. ^{13}C NMR and IR studies showed that the amine additive does not act as a ligand, but rather interacts weakly with a phenolic hydrogen of the binaphthol to form a hydrogen bond. The axial chirality of the binaphthol is thought to be transferred via the hydrogen bonds to the amine part, which shields one side of the dienophile efficiently. Of the lanthanide triflates investigated, $Yb(OTf)_3$ was found to be the most effective catalyst.

Another noteworthy feature of this reaction is that both enantiomers of the Diels-Alder adducts can be stereoselectively synthesized by using a single chiral source, (*R*)-binaphthol, and selection of the appropriate achiral ligand. In the reaction of crotonoyloxazolidinone and cyclopentadiene, the (2*S*,3*R*) enantiomer is formed stereoselectively (95% ee) in the presence of chiral catalyst **33**. On the other hand, on addition of 3-phenylacetylacetone to catalyst **33** the principle isomer was changed from the (2*S*,3*R*) isomer to its (2*R*,3*S*) enantiomer, the enantiomeric excess of which was 81%. 3-Phenylacetylacetone, which is a good bidentate ligand for lanthanides, would bind the site where crotonoyloxazolidinone originally coordinated to the chiral catalyst. The crotonoyl imide then has to bind to the other site of the catalyst, where the opposite enantioface would be exposed [51b,c] (Scheme 1.64).

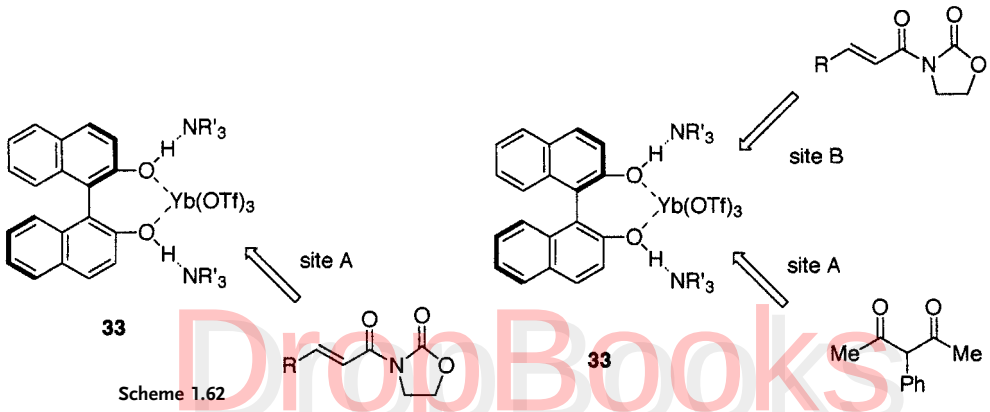


Scheme 1.61

Nakagawa and coworkers reported a chiral ytterbium catalyst **34** which was prepared from 1,1′-(2,2′-bisacylamino)binaphthalene and $Yb(OTf)_3$ in the presence of diisopropylethylamine by a method similar to that used for Kobayashi's chiral ytterbium reagent [52] (Scheme 1.65, Table 1.66). The amine also plays an important role in this reaction, because racemic cycloadducts were obtained without the *tert*-amine. Reduc-

Table 1.26 Asymmetric Diels-Alder reactions of cyclopentadiene catalyzed by **33** [51 b]

R	*Additive*	*Temp. (°C)*	*Yield (%)*	*endo/exo*	*(2S,3R)/(2R,3S)*
Me	No	0	77	89:11	97.5:2.5
	Yes	23	83	93:7	9.5:90.5
n-Pr	No	23	81	80:20	91.5:8.5
	Yes	23	81	91:9	10:90
Ph	No	23	40	81:19	91.5:8.5
	Yes	23	60	89:11	10.5:89.5



Scheme 1.62

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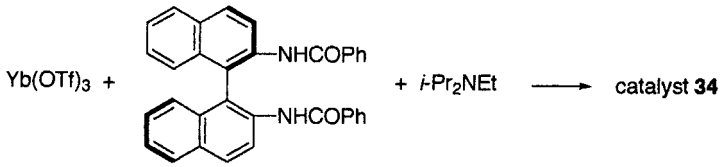
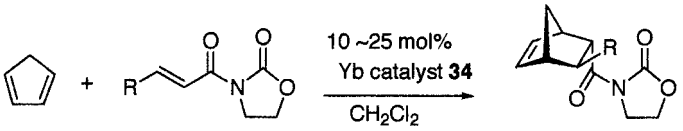
ing the amount of catalyst from 25 mol% to 5 or 10 mol% causes a decrease in chemical yield. This catalyst was highly effective in promoting the reaction of crotonoyl- and acryloyl-oxazolidinones with cyclopentadiene, giving the cyclo adducts in high optical purity.

Preparation of the chiral Yb catalyst **34**



Scheme 1.63

Shibasaki et al. reported that lithium-containing, multifunctional, heterobimetallic catalysts such as $LaLi_3$tris((*R*)-6,6′-dibromobinaphthoxide) **35**, with moderate Lewis acidity in non-polar solvents, promote the asymmetric Diels-Alder reaction to give cycloadducts in high optical purity (86% ee) [53] (Scheme 1.67). The lithium

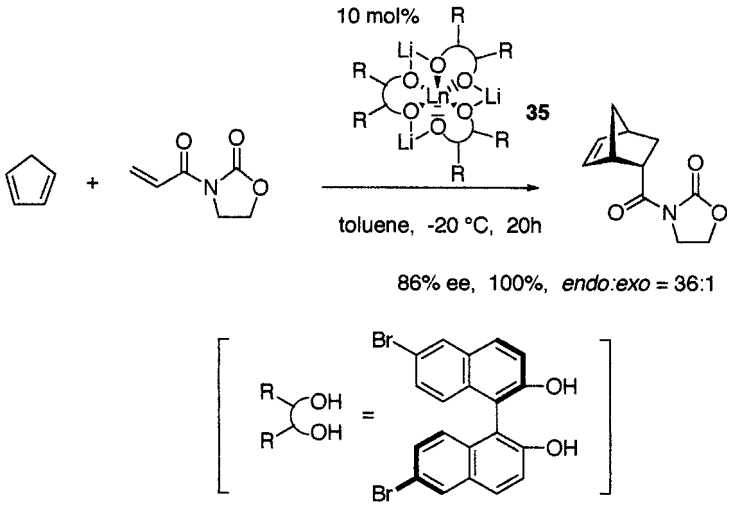


Scheme 1.64

Table 1.27 Asymmetric Diels-Alder reactions of cyclopentadiene catalyzed by **34** [52]

R	*Temp. (°)*	*Time (h)*	*Yield (%)*	*trans/cis*	*ee (%)*
H	0	0.33	99	91:9	88
Me	0	4	97	91:9	>98

atoms in these heterobimetallic complexes were found to act as a Lewis acid, and the two bromine atoms of the ligand increase the Lewis acidity of the catalyst. Of the lanthanide metals screened, lanthanum gave the best results.

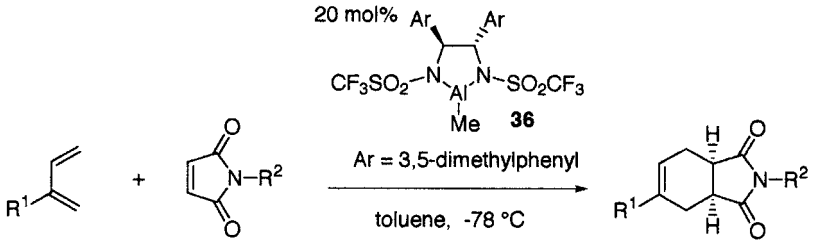


Scheme 1.65

1.2.4
The Asymmetric Diels-Alder Reaction of other Dienophiles

Several highly enantioselective Diels-Alder reactions are known for which the dienophile does not fit any of the above classes. Corey and coworkers applied the chiral aluminum reagent **36** with a C_2-symmetric stilbenediamine moiety (vide supra) to the Diels-Alder reaction of maleimides as dienophiles [54] (Scheme 1.68). In most asymmetric Diels-Alder reactions the reactants are usually relatively simple dienes such as cyclopentadiene or monosubstituted butadienes, and unsym-

metrical dienophiles such as acrylic or substituted acrylic derivatives. To achieve enantioselectivity in the Diels-Alder reaction of maleimide, a C_{2v}-symmetric *Z*-dienophile, enantioselectivity requires dissymmetry in the diene, and this is the first example of this type of system. The Diels-Alder reaction of 2-methoxy-1,3-butadiene and *N,O*-tolylmaleimide in the presence of the chiral aluminum catalyst **36** gave the adduct in 98% yield and 93% ee. *ortho* Substitution on the *N*-aryl moiety is indispensable for high enantioselectivity. The coordination of the catalyst at lone pair "a" would be necessary for high enantioselectivity, whereas the bulky aryl group effectively blocks coordination at lone pair "b" (Fig. 1.9). The chiral cycloadduct obtained was elegantly transformed to gracilins **B** and **C** [55] (Scheme 1.69).



R^1 = OMe, R^2 = *o*-$CH_3C_6H_4$; 93% ee, 98%
R^1 = Me_3SiCH_2, R^2 = *o*-$CMe_3C_6H_4$; 95% ee, 89%

Scheme 1.66

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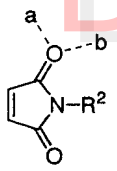
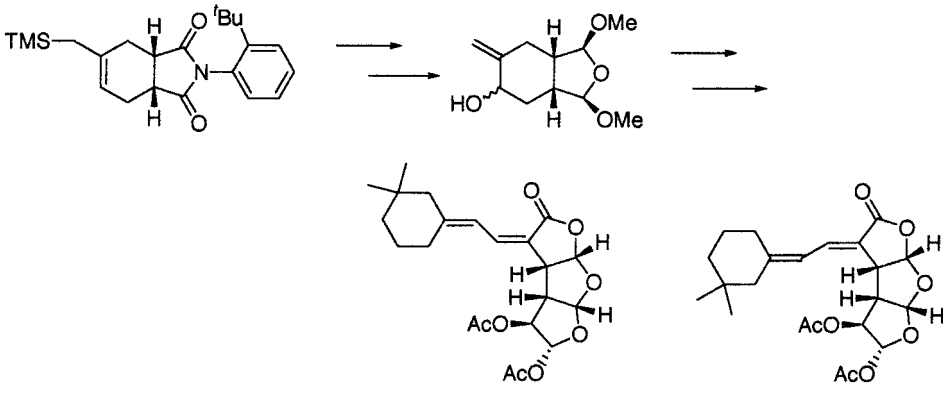
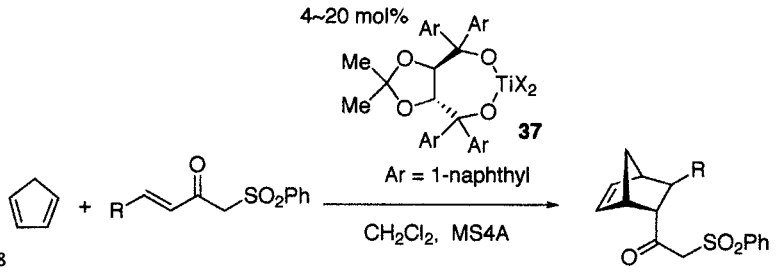


Fig. 1.9 Lone pairs on maleimide



Scheme 1.67 gracilin B gracilin C

Wada and coworkers applied TADDOL-$TiCl_2$(*O*-*i*-Pr)$_2$ catalyst **37** to the Diels-Alder reaction of (*E*)-1-phenylsulfonyl-3-alken-2-ones as dienophiles [56] (Scheme 1.70, Table 1.28). The *β*-sulfonyl ketone, which acts as a bidentate ligand for the chiral titanium reagent, reacts with cyclopentadiene to afford the cycloadduct in high optical purity. Because the phenylsulfonyl-methyl group can be transformed by reductive desulfonylation to the methyl group in good yield, this present dienophile can be regarded as an alkenyl methyl ketone equivalent.



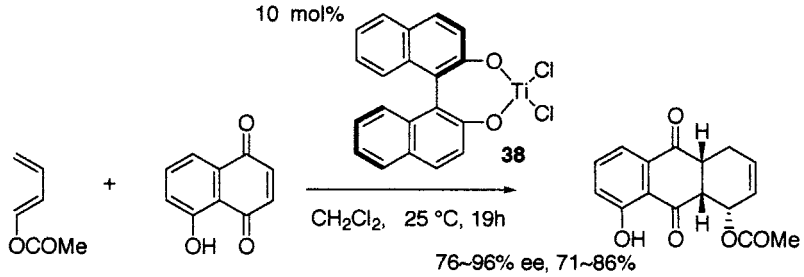
Scheme 1.68

Table 1.28 Asymmetric Diels-Alder reactions catalyzed by **37** [56]

R	*X*	*Yield (%)*	*endo/exo*	*ee (%)*
Me	Cl	80	>99:1	>99
n-Pr	Br	90	>99:1	94
Ph	Br	65	83:17	78

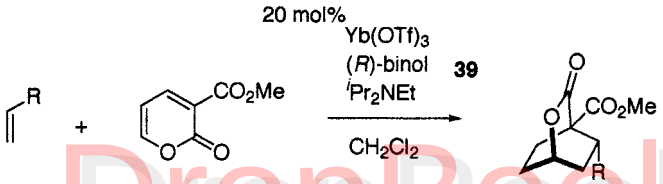
Mikami and coworkers applied a chiral BINOL (binaphthol)-$TiCl_2$(*O*-*i*-Pr)$_2$ complex **38** to the asymmetric Diels-Alder reaction of 5-hydroxynaphthoquinone (juglone) with butadienyl acetate [57] (Scheme 1.71). The crucial finding was that the absence of molecular sieves is essential for high enantioselectivity, whereas their presence is necessary for the formation of the chiral titanium catalyst from BINOL and $TiCl_2$(*O*-*i*-Pr)$_2$. In the presence of molecular sieves, however, the Diels-Alder cycloadduct was obtained in only 9% ee. The molecular sieves-free BINOL-$TiCl_2$(*O*-*i*-Pr)$_2$ complex, which was prepared by centrifugation of the suspension and decanting, gave cycloadducts in high optical purity which are useful chiral building blocks for the synthesis of anthracyclines and tetracyclines. The authors have pointed out that the enantioselectivity is somewhat variable (76–96% ee), and is very sensitive to the activity of the catalyst.

The inverse electron-demand Diels-Alder reaction is also accelerated by Lewis acids, but the successful application of chiral Lewis acids to this kind of Diels-Alder reaction is very rare. Marko and coworkers applied Kobayashi's catalyst system (Yb(OTf)3-BINOL-amine) to the Diels-Alder reaction of 3-methoxycarbonyl-2-pyrone with vinyl ether or sulfide [58] (Scheme 1.72, Table 1.29). A bulky ether or



Scheme 1.69

sulfide group is essential for success, with adamantyl vinyl ether and phenyl vinyl sulfide giving adducts in high enantiomeric excess. The chiral cycloadducts obtained are synthetically useful because of their easy transformation to chiral cyclohexadienes upon mild thermolysis.



Scheme 1.70

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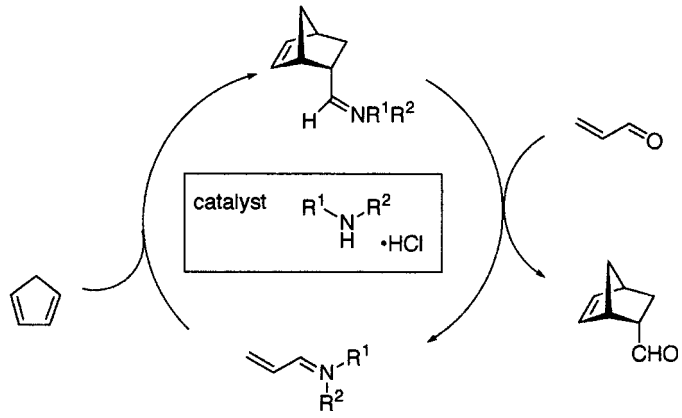
Table 1.29 Asymmetric inverse electron demand Diels-Alder reactions catalyzed by **39** [58]

R	*Yield (%)*	*ee (%)*
O-cyclohexyl	91	82
O-adamantyl	97	85
SPh	91	>95

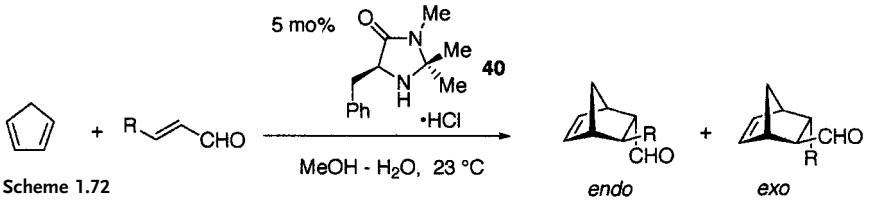
1.3 The Asymmetric Catalytic Diels-Alder Reaction Catalyzed by Base

In all the reactions described so far a chiral Lewis acid has been employed to promote the Diels-Alder reaction, but recently a completely different methodology for the asymmetric Diels-Alder reaction has been published. MacMillan and coworkers reported that the chiral secondary amine **40** catalyzes the Diels-Alder reaction between *a,β*-unsaturated aldehydes and a variety of dienes [59]. The reaction mechanism is shown in Scheme 1.73. An *a,β*-unsaturated aldehyde reacts with the chiral amine **40** to give an iminium ion that is sufficiently activated to engage a diene reaction partner. Diels-Alder reaction leads to a new iminium ion, which upon hydrolysis af-

fords the cycloaddition product and regenerates the chiral amine catalyst. Of the several amines examined, **40** was found to be optimum. This Diels-Alder reaction has wide generality in respect of both diene and dienophile (Scheme 1.74, 1.75, Table 1.30, 1.31). Acrolein, crotonaldehyde, and cinnamaldehyde react with cyclopentadiene to give addition products in high optical purity. Cyclohexadiene, isoprene, and 1-methoxybutadiene can all be successfully employed as the diene component.



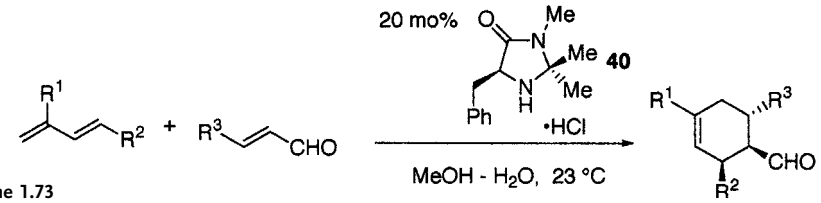
Scheme 1.71



Scheme 1.72

Table 1.30 Asymmetric Diels-Alder reactions of cyclopentadiene catalyzed by **40** [59]

R	*Time (h)*	*Yield (%)*	*endo/exo*	*endo ee (%)*	*exo ee (%)*
Me	16	75	1:1	90	86
Pr	14	92	1:1	90	86
Ph	21	99	11.3	93	93



Scheme 1.73

Table 1.31 Asymmetric Diels-Alder reactions catalyzed by **40** [59]

R^1	R^2	R^3	*Yield (%)*	*endo/exo*	*ee (%)*
Me	H	H	84	–	89
Ph	H	H	90	–	83
Ph	H	Me	75	–	90
Me	Me	H	75	5:1	90
H	OAc	H	72	11:1	85

1.4 Conclusions

Many chiral metal complexes with Lewis acid properties have been developed and applied to the asymmetric Diels-Alder reaction. High enantioselectivity is, of course, one of the goals in the development of these catalysts. Enantioselectivity is not, however, the only factor important in their design. Other important considerations are:

(i) the generality of the reaction, with regard to the combinations of diene and dienophile that can be used;
(ii) chemical yield;
(iii) diastereomer selectivity (*endo*/*exo*);
(iv) ease of preparation of the ligand and catalyst;
(v) catalyst stability;
(vi) catalyst recovery; and
(vii) reaction conditions (reaction temperature and time).

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Among the many chiral Lewis acid catalysts described so far, not many practical catalysts meet these criteria. For *a*,*β*-unsaturated aldehydes, Corey's tryptophan-derived borane catalyst **4**, and Yamamoto's CBA and BLA catalysts **3**, **7**, and **8** are excellent. Narasaka's chiral titanium catalyst **31** and Evans's chiral copper catalyst **24** are outstanding chiral Lewis acid catalysts of the reaction of 3-alkenoyl-1,2-oxazolidin-2-one as dienophile. These chiral Lewis acid catalysts have wide scope and generality compared with the others, as shown in their application to natural product syntheses. They are, however, still not perfect catalysts. We need to continue the endeavor to seek better catalysts which are more reactive, more selective, and have wider applicability.

1.5 Appendix

Below is a table of asymmetric Diels-Alder reactions of *a*,*β*-unsaturated aldehydes catalyzed by chiral Lewis acids **1**–**17** (Fig. 1.10, 1.11). The amount of catalyst, reaction conditions (temperature, time), chemical yield, *endo*/*exo* selectivity, and optical purity are listed (Table 1.32).

Table 1.32 Asymmetric Diels-Alder reactions of α,β-unsaturated aldehydes

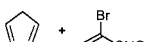
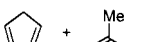
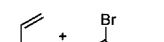
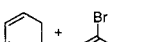
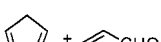
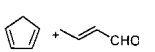
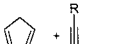
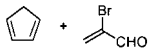
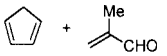
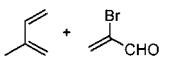
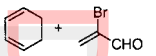
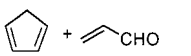
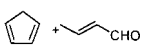
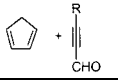
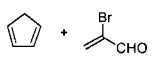
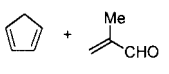
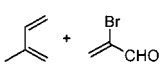
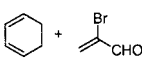
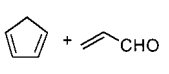
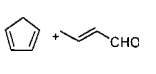
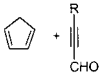
Catalyst							
1 [1]		0.15 equiv. –78 °C quant, 2:98 72% ee			27% ee		
2 [4]		0.005 equiv. –78 °C, 4 h 100%, 3:97 97.7% ee					
3 [5]	0.1 equiv. –78 °C, 10 h quant, 6:94 98% ee	0.1 equiv. –78 °C, 6 h 85%, 11:89 96% ee	0.1 equiv. –40 °C, 12 h 52% 87% ee		0.1 equiv. –78 °C, 14.5 h 90%, 88:12 84% ee	0.1 equiv. –78 °C, 10 h 53%, 90:10 2% ee	
4 [6]	0.05 equiv. –78 °C, 1 h 95%, 4:96 99% ee	92% ee	0.05 equiv. –40 °C, 48 h 76% 92% ee		40% ee		
5 [7]		0.15 equiv. –78 °C 88%, 4:96 95% ee					
6 [8]		0.2 equiv. –78 °C, 12 h 84%, >1:99 97% ee					

Table 1.32 Continued

Catalyst							
7 [10]	0.05 equiv. –78 °C, 4 h >99%, >1:99 >99% ee	0.1 equiv. –78 °C >99%, >1:99 99% ee	0.1 equiv. –40 °C >99% 98% ee		0.1 equiv. –78 °C 91%, 91:9 40% ee	0.1 equiv. –78 °C 12%, 89:11 36% ee	R = H 0.2 equiv. –78 °C 63% 88% ee
8 [10]	0.05 equiv. –78 °C >99%, 10:90 >99% ee		0.1 equiv. –78 °C 95% >99% ee	0.1 equiv. –78 °C 65%, 90:10 95% ee	0.05 equiv. –78 °C 84%, 97:3 95% ee	0.2 equiv. –78 °C 94%, 90:10 95% ee	
9 [11, 12]	0.1 equiv. –94 °C, 2 h 99%, 9:91 98% ee	0.1 equiv. –94 °C, 2 h 99%, 12:88 90% ee	0.1 equiv. –94 °C, 1 h 99% 96% ee	0.1 equiv. –94 °C, 2 h 99%, 96:4 93% ee			R = TMS 0.2 equiv. –94–78 °C 68% 87% ee
10 [16]		0.1 equiv. –78 °C, 70 h 75%, 1:99 94% ee			0.1 equiv. –78 °C, 3.5 h 70%, 85:15 96% ee	0.1 equiv. –40 °C, 50 h 76%, 70:30 95% ee	
11 [17]	0.1 equiv. –78 °C, 0.5 h 94%, 1:67 93% ee		0.1 equiv. –78 °C, 48 h quant 90% ee				

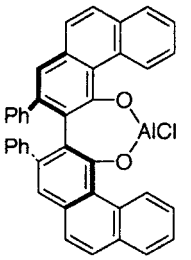
Chemistry Books

Table 1.32 Continued

Catalyst							
12 [18]			0.05 equiv. –30 °C, 1–3 h 95% 95% ee				
13 [19]	0.05 equiv. –20 °C, 2 h 83%, 6:94 95% ee	0.05 equiv. –20 °C, 20 h 83%, 2:98 97% ee		0.05 equiv. –20 °C, 20 h 86%, 90:10 >99% ee	0.05 equiv. –30 °C, 16 h 76%, 66:34 81% ee		
14 [20]	0.05 equiv. –20 °C, 2 h 93%, 7:93 92% ee	0.05 equiv. –20 °C, 22 h 91%, 3:97 92% ee		0.05 equiv. –20 °C, 21 h 29%, 90:10 95% ee			
16 [22]	0.1 equiv. –40 °C, 48 h 93%, 3:97 86% ee						
17 [23]	0.05 equiv. –78 °C, 12 h >95% conv., 2:98 96% ee	0.05 equiv. –40 °C, 8 h >95% conv., 3:97 92% ee			0.05 equiv. –20 °C, 18 h 96:4 85% ee		

For each reaction the data given are:
Amount of catalyst;
Temperature, time;
Yield, *endo/exo*; and
Optical yield.

1



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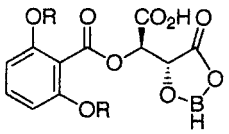
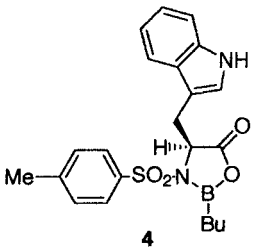


3 R = Me or *i*-Pr



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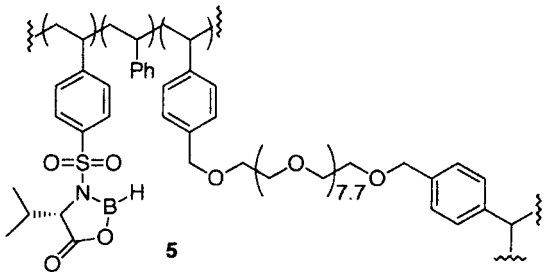
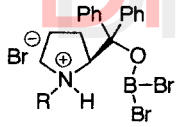


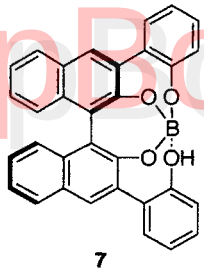
5

DropBooks

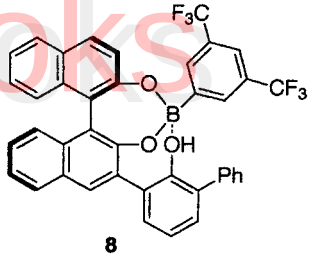


R = Me or Bn

6



7



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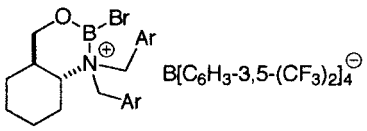
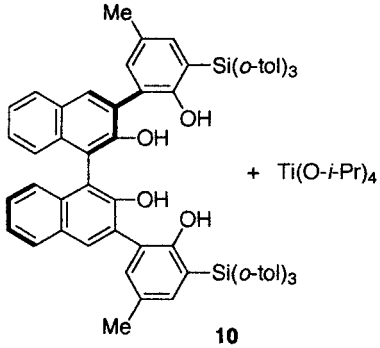


Ar = 3,5-dimethylphenyl

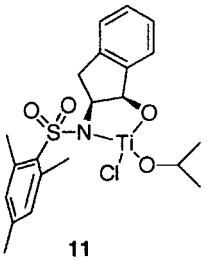
9



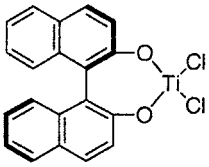
+ $Ti(O\text{-}i\text{-}Pr)_4$

10

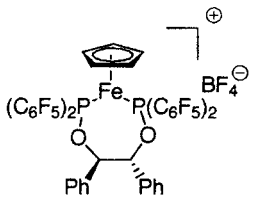
Fig. 1.10



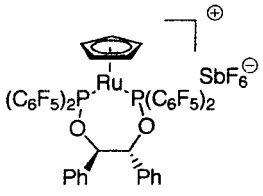
11



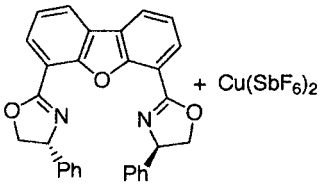
12



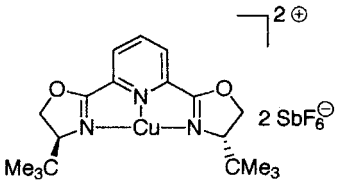
13



14



16



17

Fig. 1.11

Acknowledgment

I would like to thank Professors E. J. Corey and K. Narasaka for giving me a chance to work with super-reactive chiral catalyst **9** and TADDOL-based chiral titanium catalyst **31**, respectively.

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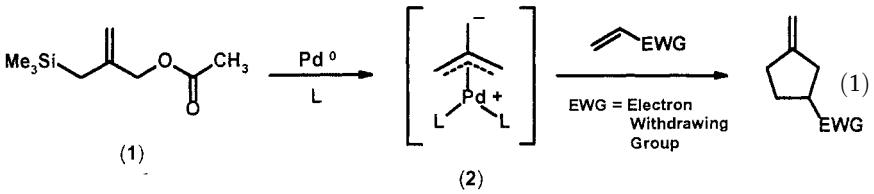
2
Recent Advances in Palladium-catalyzed Cycloadditions involving Trimethylenemethane and its Analogs

Dominic M.T. Chan

2.1
General Introduction

The discovery of palladium trimethylenemethane (TMM) cycloadditions by Trost and Chan over two decades ago constitutes one of the significant advancements in ring-construction methodology [1]. In their seminal work it was shown that in the presence of a palladium(0) catalyst, 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate (**1**) generates a TMM-Pd intermediate (**2**) that serves as the all-carbon 1,3-dipole. It was further demonstrated that (**2**) could be efficiently trapped by an *electron-deficient olefin* to give a methylenecyclopentane via a [3+2] cycloaddition (Eq. 1).



Since its inception, considerable progress has been made by the laboratories of Trost and others in expanding this TMM cycloaddition chemistry. The advancements include the development of substituted analogs, improved catalytic systems, other TMM precursors, and analogous cycloaddition reactions involving both inter- and intramolecular systems. In addition to two reviews by Trost [2], different aspects of the area were surveyed by Inoue in 1985, by Chan in 1989, and by Lautens in 1996 [3–5]. This chapter will focus only on the TMM chemistry using Trost's approach, even though other methodologies are also available [3, 4]. It will provide some brief background information, but will concentrate primarily on recent advances. Both published works in the literature and unpublished results from Trost's laboratory will be presented. Readers are encouraged to peruse the aforementioned reviews for more comprehensive surveys of the area in its earlier development.

2.2
Mechanism for [3+2] Carbocyclic Cycloaddition

The originally proposed mechanism for the methylenecyclopentane formation depicted in Scheme 2.1 involves the initial formation of a π-allyl intermediate (**3**) which then undergoes a facile elimination of trimethylsilyl acetate to generate the palladium-bound TMM complex (**2**) [6]. An X-ray crystallographic analysis of a stable TMM-Pd complex prepared by a different route indicates that the ligand binds in an unsymmetrical η^3 mode, in contrast to virtually all other metal complexes of this fragment which have symmetrical η^4 binding mode [7]. This observation is consistent with a theoretical study that also indicates that one of the carbon termini of the TMM ligand carries a more negative charge [8]. In the methylenecyclopentane formation process, it is believed that it is this carbon terminal which Michael adds to the electron-deficient olefin to first generate an intermediate complex (**4**). Subsequent intramolecular cyclization of (**4**) gives rise to the five-membered ring and regenerates the catalyst (Scheme 1). This stepwise, non-concerted mechanism has withstood the test of time, as it is also used to explain the lack of stereospecificity in cycloadditions with *cis* olefins [1a, 9].

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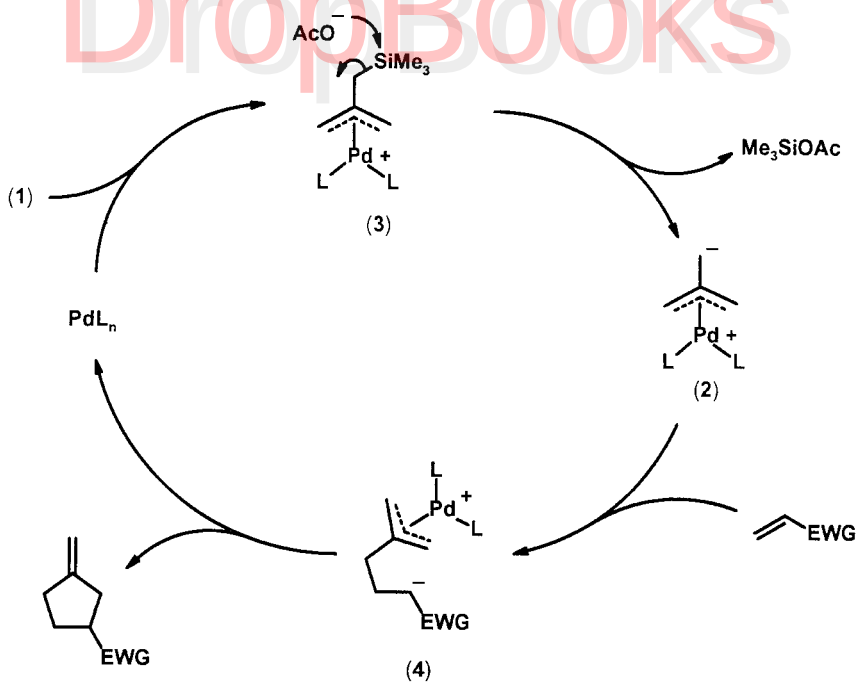
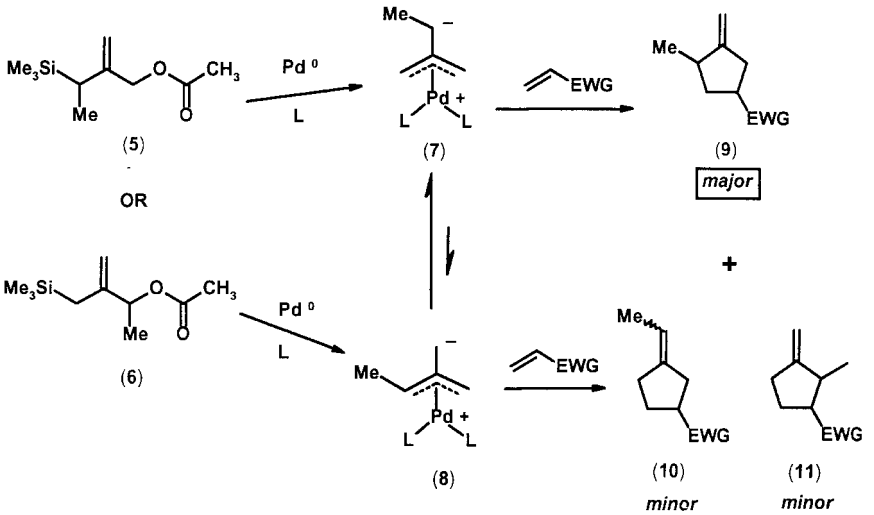


Scheme 2.1 Proposed mechanism for TMM [3+2] cycloaddition with an electron deficient olefin

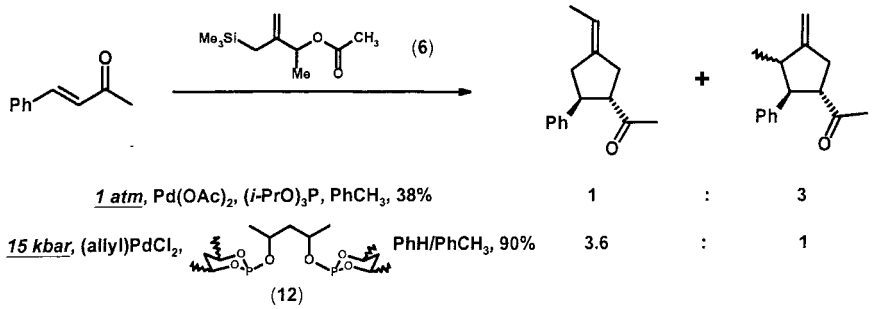
2.3
Dynamic Behavior of TMM-Pd Complexes

A deuterium-labeling study of (**1**) verifies that all three methylene termini can scramble in the unsymmetrical TMM-Pd complex (**2**) [10]. This dynamic behavior, which can be envisioned as having the palladium center whirl around the ligand, is also manifested in substituted systems. Cycloadditions of either of the methyl precursor (**5**) or (**6**) give the *same major product* (**9**) (80–100% depending on the nature of the olefin). Again, this observation is explained by a faster equilibration (compared with cycloaddition) between the two initially formed TMM complexes (**7**) and (**8**), and that (**7**) is more reactive towards addition to the olefin (Scheme 2.2). Interestingly, the theoretical study by Fenske suggests that complex (**7**) is also favored thermodynamically [8]. The same regioselectivity is observed with other substituted systems even when the methyl group is replaced with an electron-withdrawing group, e.g. CN and CO_2Me, electron-donating group, e.g. OAc, or a bulky substituent, e.g. $SiMe_3$ [4].



Scheme 2.2 Proposed mechanism for substituted TMM [3+2] cycloaddition

Under high pressure, the reaction favors the formation of kinetic adducts (**10**) and (**11**) with precursor (**6**). Further regioselectivity and yield enhancement could be achieved with the bidentate phosphite ligand tpdp (**12**) as illustrated in Scheme 2.3 [11].



Scheme 2.3 Substituted TMM [3+2] cycloaddition at ambient pressure and under high pressure

2.4
Application in Organic Synthesis

2.4.1
General Comment

The use of TMM [3+2] methodology to construct five-membered carbocyclic rings offers many advantages. A wide range of electron-deficient alkenes can be used as acceptor with excellent yields. These include α,β-unsaturated systems such as esters, amides, ketones, nitriles, and sulfones. The cycloaddition is often highly diastereoselective and the resulting exocyclic methylene group is useful for further structural elaboration. Reaction condition simply entails heating a solution of the TMM precursor and the substrate with the palladium catalyst under reflux in an aprotic solvent under an inert atmosphere.

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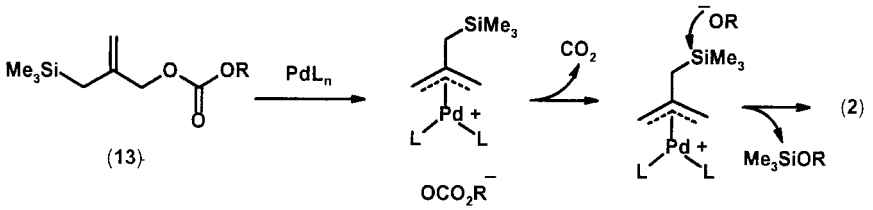
Recent discoveries have further expanded the synthetic potential of TMM cycloaddition approach. For example, the carbonate (**13**) has been developed as another convenient source of TMM. In this case, the desilylation is initiated by the alkoxide, which is generated from the decarboxylation of the carbonate leaving group (Scheme 2.4). The higher reactivity of this type of precursor can be advantageous in facilitating the cycloaddition (vide infra). Furthermore, trialkyl phosphite has been found to be more efficient than triphenylphosphine as the ligand in many cycloadditions.



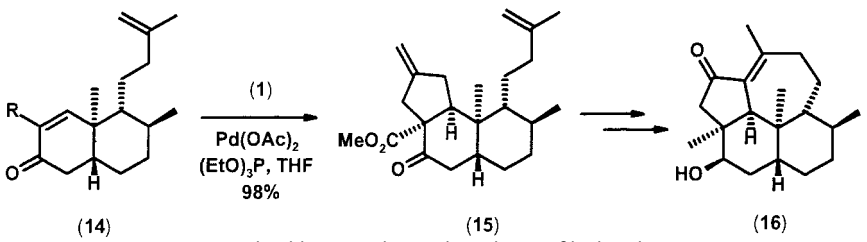
Scheme 2.4 TMM-Pd formation from carbonate precursor (**13**)

Other advances include the construction of seven- and nine-membered rings via the analogous [4+3] and [6+3] cycloadditions with dienes and trienes respectively. Heterocycles, such as tetrahydrofurans and pyrrolidines, are accessible using carbonyl compounds and imines as substrates. The following discussion is organized around these recent discoveries. It serves to illustrate the versatility and the high degree of selectivity which are some of the distinctive features of the Pd-TMM chemistry.

2.4.2 [3+2] Cycloaddition: The Parent TMM

2.4.2.1 Recent Applications in Natural and Unnatural Product Synthesis

The parent TMM precursor (**1**), now commercially available, has played a pivotal role in the execution of many synthetic plans directed at natural and unnatural targets. Reaction of (**1**) with 2-(methoxycarbonyl)cyclohexenone (**14**, R = CO_2Me) in the presence of palladium acetate and triethyl phosphite produced the adduct (**15**) in near quantitative yield. This cycloadduct is a critical intermediate in the total synthesis of a hydroxykempenone (**16**), a component of the defensive substances secreted by termites (Scheme 2.5) [12]. In accord with a previous observation by Trost that unactivated 2-cyclohexenone reacts poorly with TMM-Pd [13], the substrate (**14**, R = Me) was essentially inert in the cycloaddition.



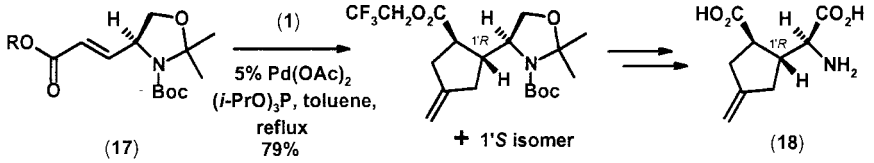
(**14**) (**15**) (**16**)

Scheme 2.5 TMM [3+2] cycloaddition in the total synthesis of hydroxykempenone (**16**)

TMM cycloaddition also provides access to structurally rigid glutamate analogs. Thus (**1**) cycloadds to α,β-unsaturated ester (**17**, R = CH_2CF_3) to give a 79% yield of a mixture of 1′*R* and 1′*S* methylenecyclopentane in 8.8 : 1.2 ratio. Further purification and transformation provided the glycine (**18**), which was shown to be a potent agonist of kainate receptors. The more electron-deficient trifluoroethyl ester is needed for efficient cycloaddition as no reaction was observed with the corresponding methyl ester (**17**, R = Me) (Scheme 2.6) [14].

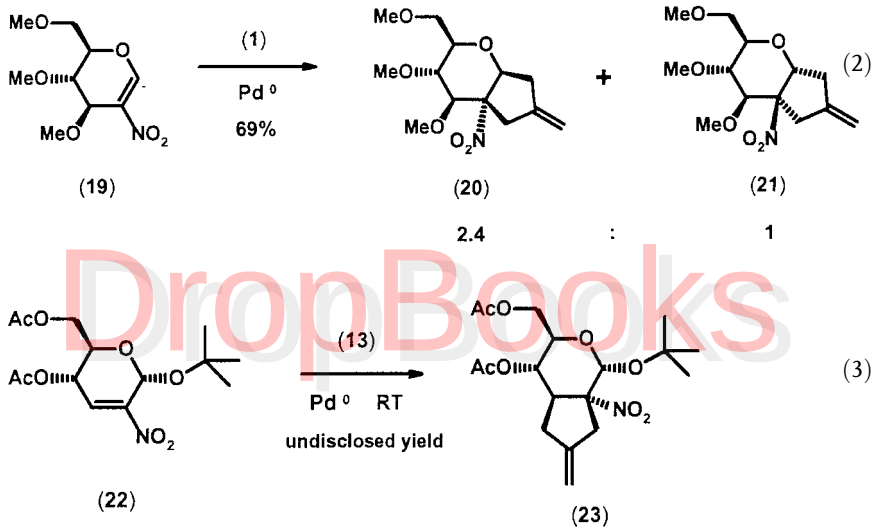
2.4.2.2 Novel Substrates for TMM Cycloaddition

Nitro-activated glycals and aromatic compounds are good acceptors for TMM-Pd chemistry. The nitroglycal (**19**) reacts with (**1**) to give a 2.4 : 1 ratio of products (**20**) and (**21**) in a combined yield of 69% (Eq. 2). Treatment of the less electron-rich



Scheme 2.6 TMM [3+2] cycloaddition in the synthesis of glutamate analog (**18**)

pseudoglycal (**22**) with the carbonate precursor (**13**, R=*t*OBu) gives a single product (**23**) at ambient temperature with an undisclosed yield (Eq. 3). In this case, the less reactive acetate (**1**) failed to participate under a variety of reaction conditions [15].



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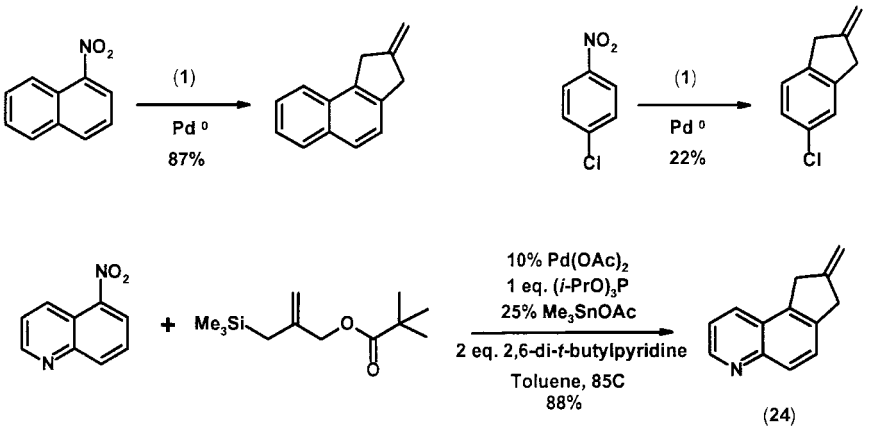
Nitroaromatics, such as 1-nitronaphthalene and 4-chloronitrobenzene, have been reported to react with the acetate (**1**) to produce cycloadducts arising from the subsequent elimination of HNO_2 [15]. Improved yields were observed with the introduction of 1.25 equiv. of 2,6-di-*t*-butylpyridine as an acid scavenger, and using the corresponding pivalate of (**1**) as the TMM precursor. While 3-nitropyridine and phenyl triflone ($PhSO_2CF_3$) failed to participate in the cycloaddition, 5-nitroquinoline did give a good yield of adduct (**24**) (Scheme 2.7) [16].

Palladium-catalyzed cycloaddition of (**1**) to C_{60} has been reported to proceed in 25% yield. Interestingly, the reaction requires the C_{60} be first treated with $(PPh_3)_4Pd$ and dppe in benzene before the introduction of (**1**) [17].

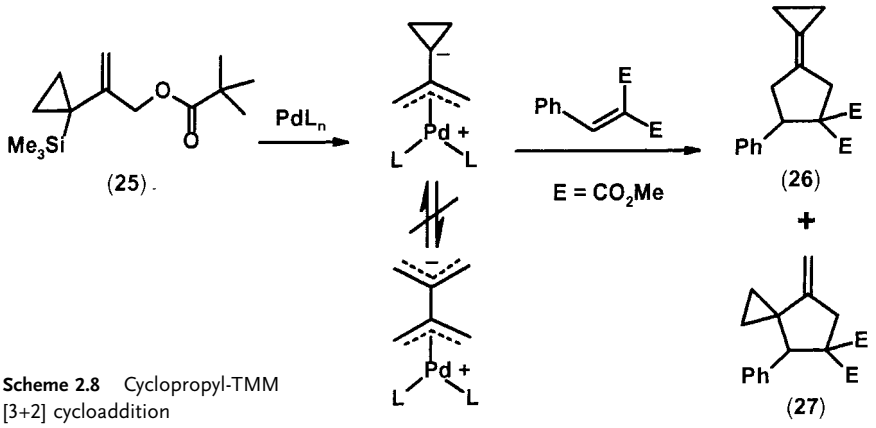


Scheme 2.7 TMM [3+2] cycloaddition with nitroaromatics

2.4.3
[3+2] Cycloaddition: Substituted TMM

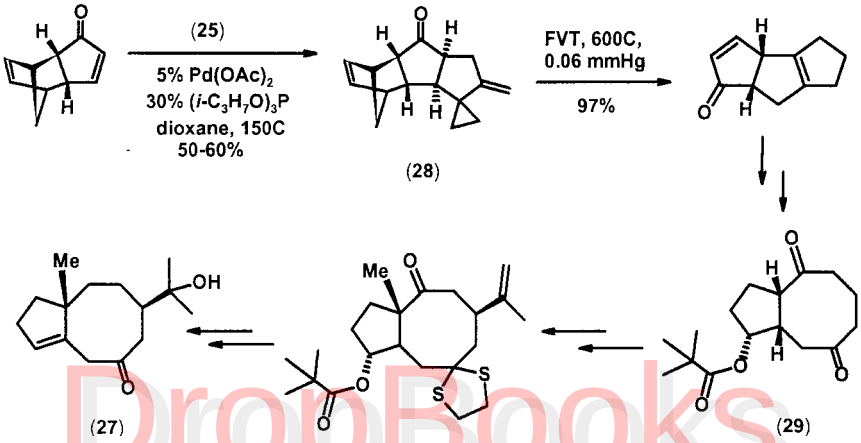
2.4.3.1 Cyclopropyl-substituted TMM

Reaction of the cyclopropyl-substituted pivalate (**25**) with dimethyl benzylidenemalonate in the presence of a palladium catalyst gave a mixture of alkylidenecyclopropane (**26**) and vinylcyclopropane (**27**). The ratio of these two adducts is found to be quite sensitive to the choice of ligand and solvent. While triisopropyl phosphite favors the formation of the methylenecyclopropane (**26**), this selectivity is completely reversed with the use of the bidentate phosphite ligand dptp (**12**). Interestingly there was no evidence for any products that would have derived from the ring opening of the cyclopropyl-TMM intermediate (Scheme 2.8) [18].



Scheme 2.8 Cyclopropyl-TMM [3+2] cycloaddition

Adducts derived from cyclopropyl-TMM reactions are versatile synthetic intermediates. Alkylidenecyclopropanes have been proven useful in further Pd-catalyzed transformations [4]. On the other hand, vinylcyclopropanes can undergo smooth thermal ring-expansion to cyclopentenes. Thus, a total synthesis of 11-hydroxyjasionone (**27**) was achieved with the cyclopropyl-TMM cycloaddition as the crucial step, and the thermal rearrangement of the initial adduct (**28**) as an entry to the bicyclo[6.3.0]undecyl compound (**29**), a key intermediate in the synthetic sequence (Scheme 2.9) [19].



Scheme 2.9 Cyclopropyl-TMM [3+2] cycloaddition in the synthesis of 11-hydroxyjasionone (**27**)

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2.4.3.2 **Phenylthio-TMM**

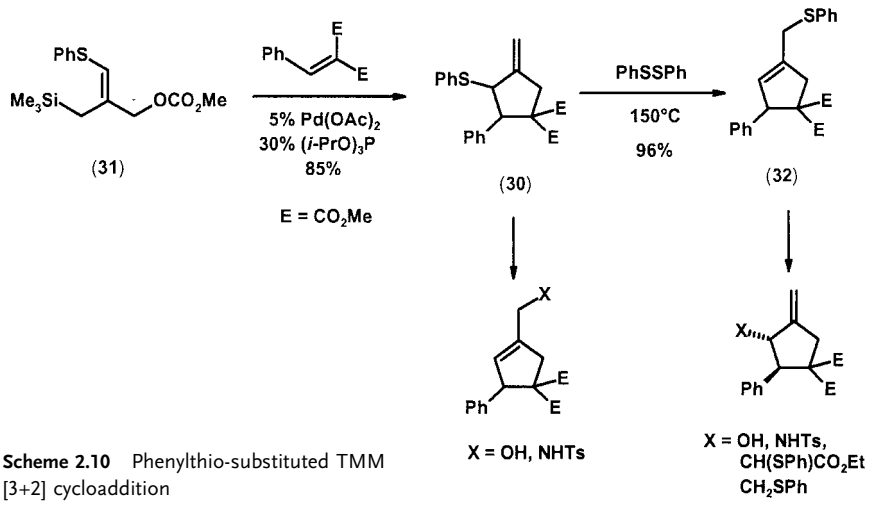
Contrary to the expectation that a sulfur-containing substituent will be a catalyst poison, a phenylthio group serves as an effective selectivity control element in TMM cycloadditions. A single regioisomer (**30**) was obtained from the carbonate precursor (**31**) in good yield. The thermodynamically more stable sulfide (**32**) is readily accessible from (**30**) via a 1,3-sulfide shift catalyzed by PhSSPh. A wide array of synthetically useful intermediates could be prepared from the sulfides (**30**) and (**32**) with simple transformations (Scheme 2.10) [20].

2.4.4

[3+2] Cycloaddition: Intramolecular Versions

2.4.4.1 **Introduction and Substrate Synthesis**

Intramolecular [3+2] cycloadditions, i.e., having the TMM moiety and the acceptor linked by a tether, have great synthetic utility in polycarbocycle construction. The construction of {5.5}, {6.5}, and {7.5}ring systems has been demonstrated with this methodology [21–25]. A number of efficient routes to acyclic precursors were developed (Scheme 2.11). The organometallic reagent (**31**), generated from 2-bromo-3-(trimethylsilyl)propene (**32**) [26], is a key component in the construction of



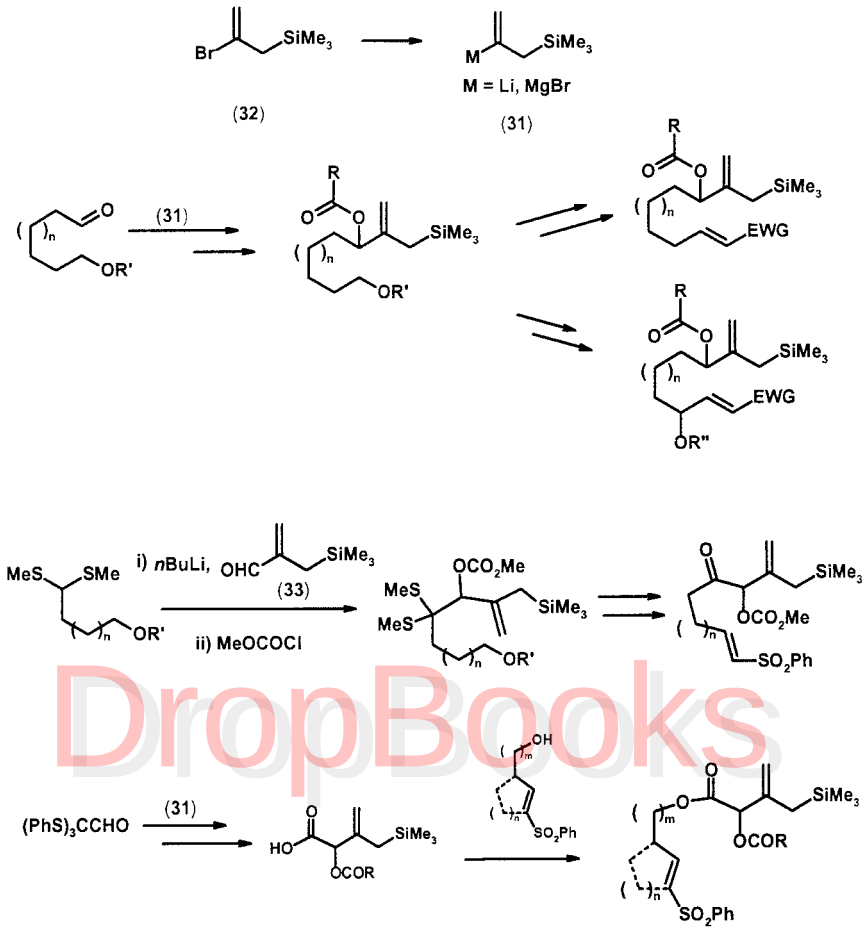
Scheme 2.10 Phenylthio-substituted TMM [3+2] cycloaddition

the TMM portion. The bifunctional aldehyde (**33**) proves useful in a lynchpin-type strategy to the requisite substrates.

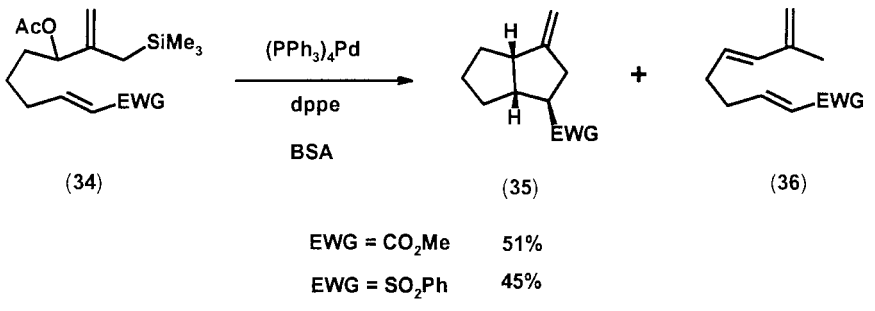
2.4.4.2 **Synthesis of Bicyclo[3.3.0]octyl Systems**

Treatment of the substrate (**34**) with catalytic $(Ph_3P)_4Pd$ and dppe provided the desired bicyclo[3.3.0]octanes (**35**) and the acetate elimination product (**36**). The choice of ligand is crucial in this case since using only dppe or Ph_3P increased the amount of (**36**). On the other hand addition of BSA (*N,O*-bis(trimethylsilyl) acetamide) minimized this side product (Scheme 2.12) [24].

Intramolecular cycloadditions of substrates with a cleavable tether have also been realized. Thus esters (**37a–37d**) provided the structurally interesting tricyclic lactones (**38–43**). It is interesting to note that the cyclododecenyl system ($n=7$) proceeded at room temperature whereas all others required refluxing dioxane. In each case, the stereoselectivity with respect to the tether was excellent. As expected, the cyclohexenyl ($n=1$) and cycloheptenyl ($n=2$) gave the *syn* adducts (**38**) and (**39**) almost exclusively. On the other hand, the cyclooctenyl ($n=3$) and cyclododecenyl ($n=7$) systems favored the *anti* adducts (**41**) and (**42**) instead. The formation of the endocyclic isomer (**39**, $n=1$) in the cyclohexenyl case can be explained by the isomerization of the initial adduct (**44**), which can not cyclize due to ring-strain, to the other π-allyl-Pd intermediate (**45**) which then ring-closes to (**39**) (Scheme 2.13) [20]. While the yields may not be spectacular, it is still remarkable that these reactions proceeded as well as they did since the substrates do contain another allylic ester moiety which is known to undergo ionization in the presence of the same palladium catalyst.



Scheme 2.11 Synthesis of substrates for intramolecular TMM [3+2] cycloadditions



Scheme 2.12 Intramolecular TMM [3+2] cycloaddition to bicyclo[3.3.0]octyl systems

2.4.4.3 Synthesis of Bicyclo[4.3.0]nonyl Systems

Perhydroindans (**46**) and (**47**) could be obtained in 73% yield from the carbonate (**48**) with only minor amounts of elimination product. The use of BSA and the triisopropyl phosphite-palladium acetate catalytic system provides further improvement. The low *cis*/*trans* selectivity in the formation of the first ring, and rapid subsequent cyclization account for the fact that the ratio of (**46**) to (**47**) is only 2:1 (Scheme 2.14). Even the presence of a bulky trialkylsiloxyl substituent adjacent to the vinyl sulfone moiety has only a minor influence on the *cis*/*trans* selectivity [24].

Introduction of an additional methyl group on the donor atom of TMM moiety gives a low 33% yield of the perhydroindans (**49**, $X=H_2$) and (**50**, $X=H_2$) with substantial production of the diene by-products [24]. However, it is still remarkable that the reaction works at all since the corresponding intermolecular cycloaddition failed. Incorporation of a carbonyl moiety adjacent to the donor carbon atom doubles the yield of the cycloadducts to 66% (Scheme 2.15). This so-called "*acyl effect*" works by making the donor carbon of the TMM unit "softer," thus facilitating the initial step of the conjugate addition, as well as inhibiting base-induced side reactions [22].

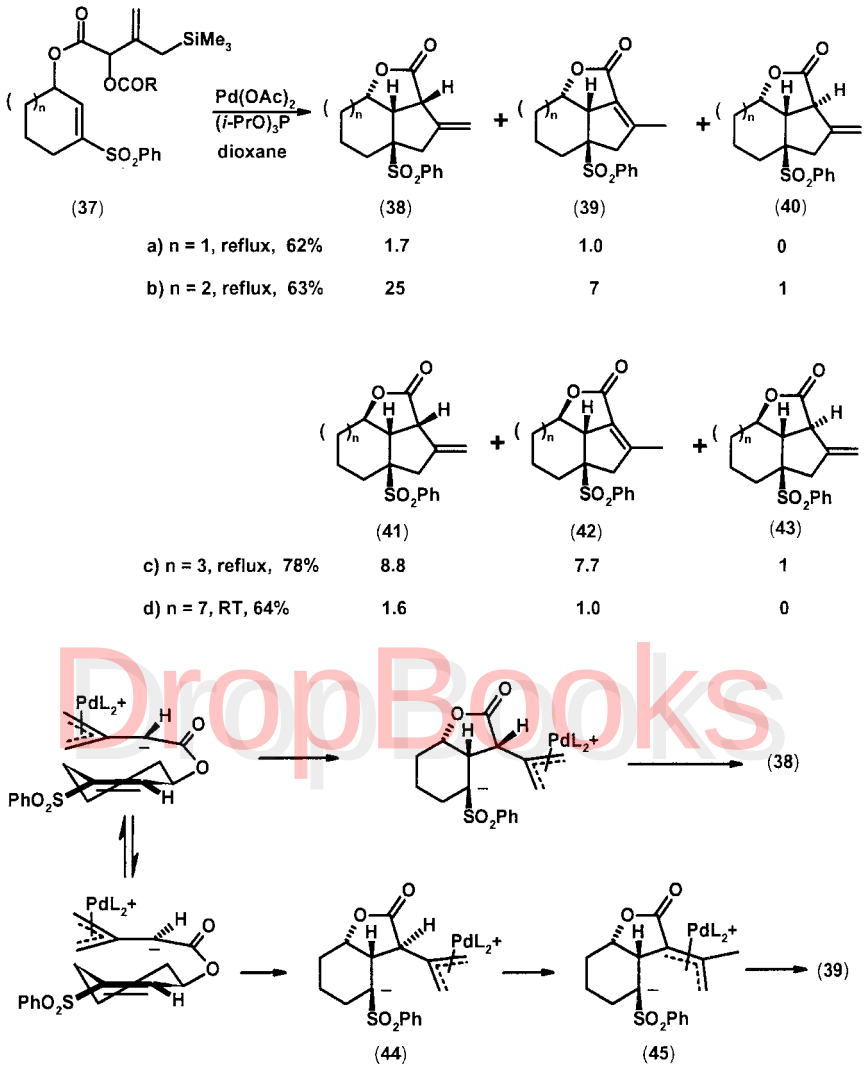
2.4.4.4 Synthesis of Bicyclo[5.3.0]decyl Systems

The "acyl effect" proves crucial in the formation of the perhydroazulene systems: cyclization can only take place with the presence of an acyl group on the TMM portion whereas the parent hydrocarbon fails. For example, treatment of substrate (**51**) with the palladium catalyst gave a mixture of the bicyclic compounds (**52**) and (**53**) in 51% yield. The formation of endocyclic olefin (**52**) is presumed to occur when the first formed (**53**) was exposed to silica gel during purification [22]. This intramolecular cycloaddition strategy was utilized in a highly diastereoselective preparation of a key intermediate (**54**) in the total synthesis of (–)-isoclavukerin A (**55**) (Scheme 2.16) [21].

2.4.5 Carboxylative Cycloadditions

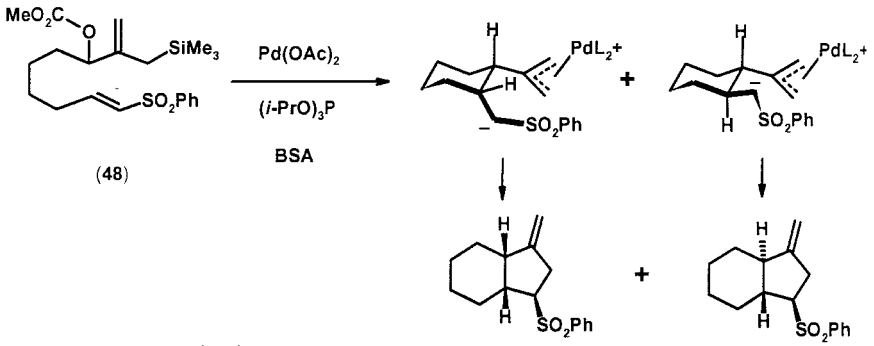
The use of carbonate precursor (**56**) allows the introduction of a carboxylic function in the cycloadduct. The proposed mechanism involves internal delivery of a Pd-bound carbon dioxide to the TMM unit as depicted in Scheme 2.17 [27, 28].

One interesting feature of this carboxylative cycloaddition is the improved efficiency with poor acceptor such as cyclohexenone. With (**1**), the high basicity of the parent TMM (**2**) often gives rise to side reaction and therefore lower yield [29]. In the carboxylated TMM intermediate (**57**, Scheme 2.17), the basicity of the carbanion center is now moderated by the adjacent ester function, thus suppressing the competing basic reaction pathways and resulting in a higher yield (Scheme 2.18) [27]. This is yet another example of the "acyl effect" discussed earlier in the intramolecular cycloaddition. Another feature is the extraordinarily high degree of

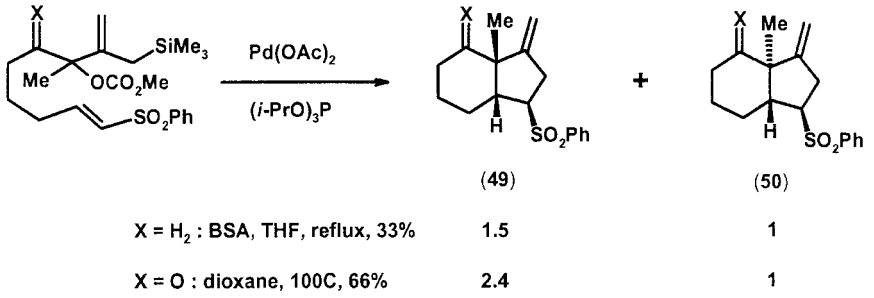


Scheme 2.13 Intramolecular TMM [3+2] cycloaddition to tricyclic lactones

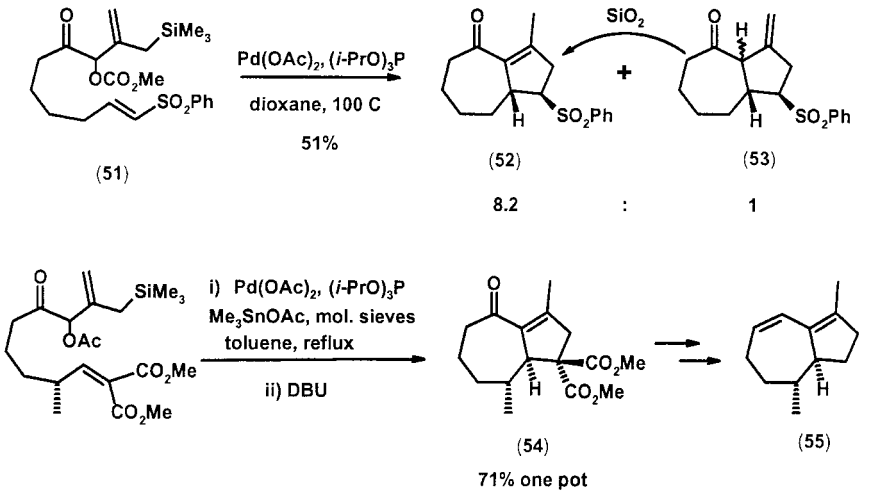
stereospecificity observed in the case of addition to α,β-unsaturated ester. While the cis olefin geometry of this type of acceptor is normally lost with the parent TMM, it is completely preserved in the cycloadduct (**58**) derived from the substrate (**59**) with precursor (**56**) (Scheme 2.18) [27].



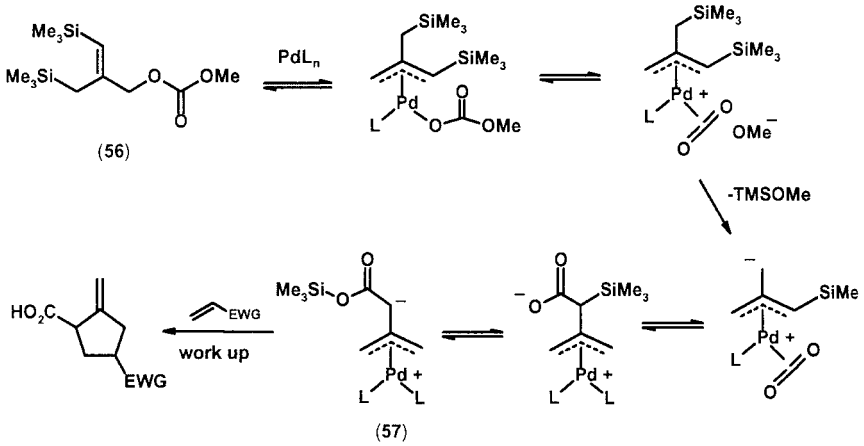
Scheme 2.14 Intramolecular TMM [3+2] cycloaddition to bicyclo[4.3.0]nonyl systems



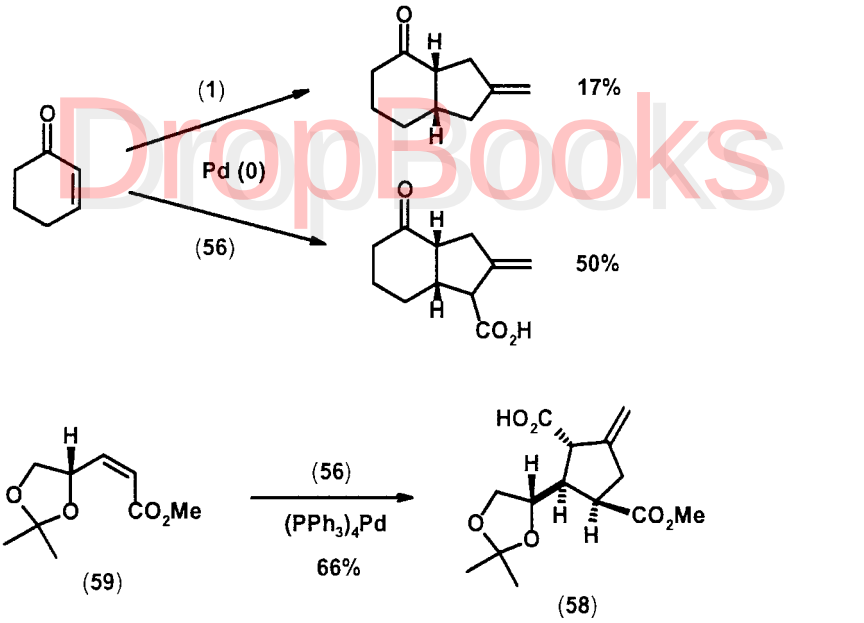
Scheme 2.15 Acyl effect in intramolecular TMM [3+2] cycloaddition



Scheme 2.16 Intramolecular TMM [3+2] cycloaddition to bicyclo[5.3.0]decanones



Scheme 2.17 Mechanism of carboxylative TMM cycloaddition



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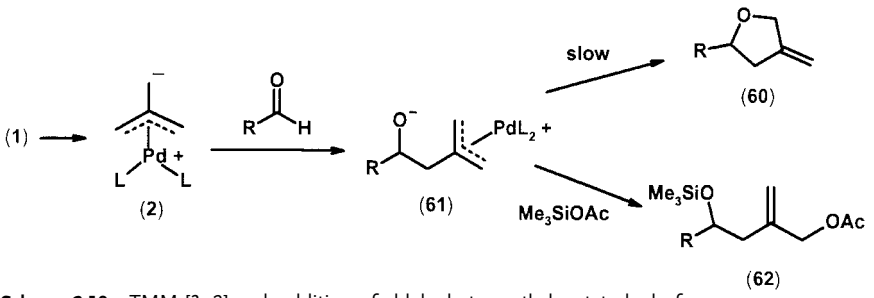
Scheme 2.18 Examples of carboxylative TMM cycloaddition

2.4.6 Carbonyl Cycloadditions

2.4.6.1 Addition to Aldehydes

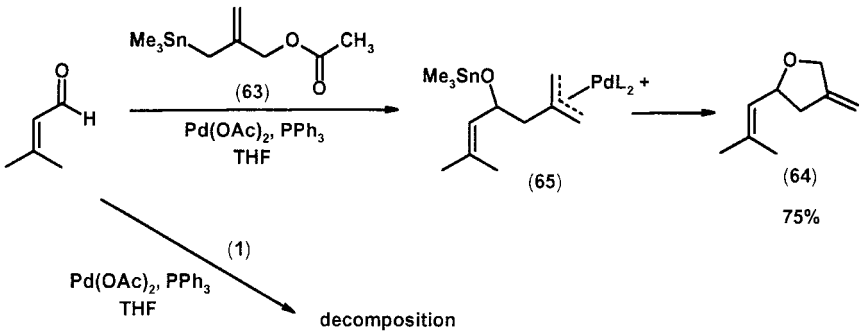
The challenge with adopting the TMM [3+2] strategy in generating a methylenetetrahydrofuran (**60**) by addition to an aldehyde lies in the poor nucleophilicity of the intermediate alkoxide (**61**) for intramolecular attack on the π-allyl ligand. Therefore, closure to the five-membered ring is often slow compared with the side reaction of silylation by TMSOAc to produce (**62**), or simply base decomposition (Scheme 2.19). For example, reaction of *n*-heptanal and cinnamaldehyde with (**1**) and catalytic $(PPh_3)_4Pd$ in refluxing THF produced only addition products (**62**, R = *n*-C_6H_{13}) and (**62**, R = PhCHCH) in 27% and 45% yield respectively [30]. However, in the presence of a triisopropyl phosphite palladium catalyst and with slow addition of (**1**) in refluxing dioxane, cinnamaldehyde does produce the desired tetrahydrofuran (**60**, R = PhCHCH) in 75% yield. A handful of other aldehydes, such as naphthaldehyde and perillaldehyde, also undergo cycloaddition when using this special condition. Nonetheless, these cycloadditions remain capricious as reaction with saturated aldehydes produced only intractable mixture [31].



Scheme 2.19 TMM [3+2] cycloaddition of aldehyde to methylenetetrahydrofuran

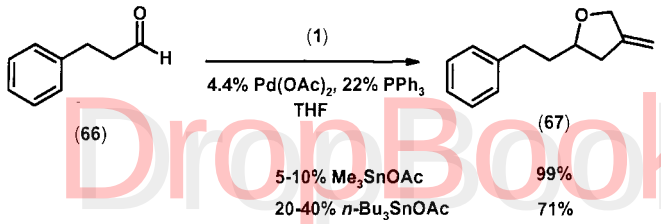
On the other hand, the corresponding tin precursor (**63**) undergoes smooth cycloaddition with a wide variety of aldehydes to produce the desired methylenetetrahydrofuran in good yields [32, 33]. Thus prenylaldehyde reacts with (**63**) to give cleanly the cycloadduct (**64**), whereas the reaction with the silyl precursor (**1**) yields only decomposition products (Scheme 2.20) [31]. This smooth cycloaddition is attributed to the improved reactivity of the stannyl ether (**65**) towards the π-allyl ligand. Although the reactions of (**63**) with aldehydes are quite robust, the use of a tin reagent as precursor for TMM presents drawbacks such as cost, stability, toxicity, and difficult purification of products.

Remarkably, the addition of only 5–10 mol% of Me_3SnOAc to the reactions of the silyl precursor (**1**) with aldehydes also cleanly produce the cycloadducts in excellent yields [31]. It then appears that the capping of the alkoxide (**61**) to form the stannyl ether in situ is efficient enough that only a catalytic amount of Me_3SnOAc is sufficient to facilitate reaction. This "*tin-effect*" greatly enhances the



Scheme 2.20 TMM cycloaddition of tin precursor (**63**) with prenylaldehyde

generality and efficiency of TMM cycloaddition to carbonyl compounds. Even the enolizable aldehyde (**66**) produced the tetrahydrofuran adduct (**67**) in quantitative yield with added Me_3SnOAc (Eq. 4). The use of *n*-Bu_3SnOAc gave a somewhat lower yield.



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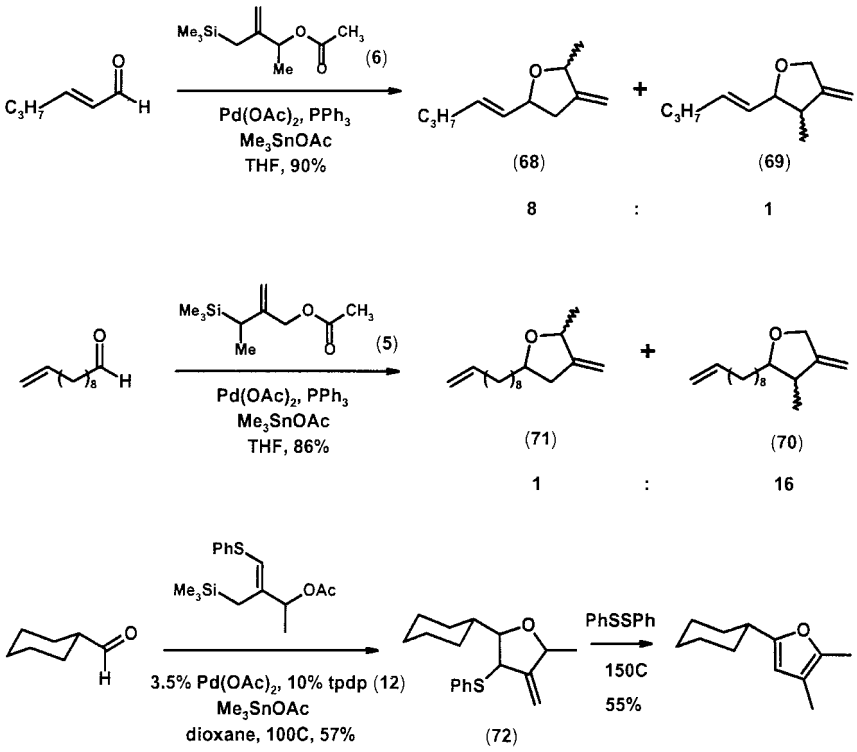
Substituted TMM complexes also cycloadd to aldehydes in the presence of a tin cocatalyst such as Me_3SnOAc and Me_3SnOTs [31]. Reaction of 2-heptenal with methyl precursor (**6**) gave a mixture of methylenetetrahydrofurans (**68**) and (**69**). This regioselectivity is reversed with 10-undecenal and methyl precursor (**5**), where adduct (**70**) now predominates over (**71**). As in the carbocyclic system, the phenylthio group also functions as a regiocontrol element in reaction with cyclohexyl aldehyde. The initially formed adduct (**72**) eliminates the element of thiophenol on attempted allyl rearrangement, and the overall process becomes a cycloaddition approach to furans (Scheme 2.21) [20].

2.4.6.2 **Addition to Ketones**

TMM cycloadditions to cyclic and conjugated ketones have also been reported (Scheme 2.22) [31]. The steric nature of the substrate does play a critical role in determining product formation. Thus the cyclic ketone (**73**) produced 55% yield of the tetrahydrofuran, but no cycloadduct could be obtained from the cyclic ketone (**74**). The enone (**75**) gave only carbonyl cycloaddition, whereas enone (**76**) yielded only olefin adduct. Interestingly, both modes of cycloaddition were observed with the enone (**77**). The ynone (**78**) also cycloadds exclusively at the carbonyl function [34].



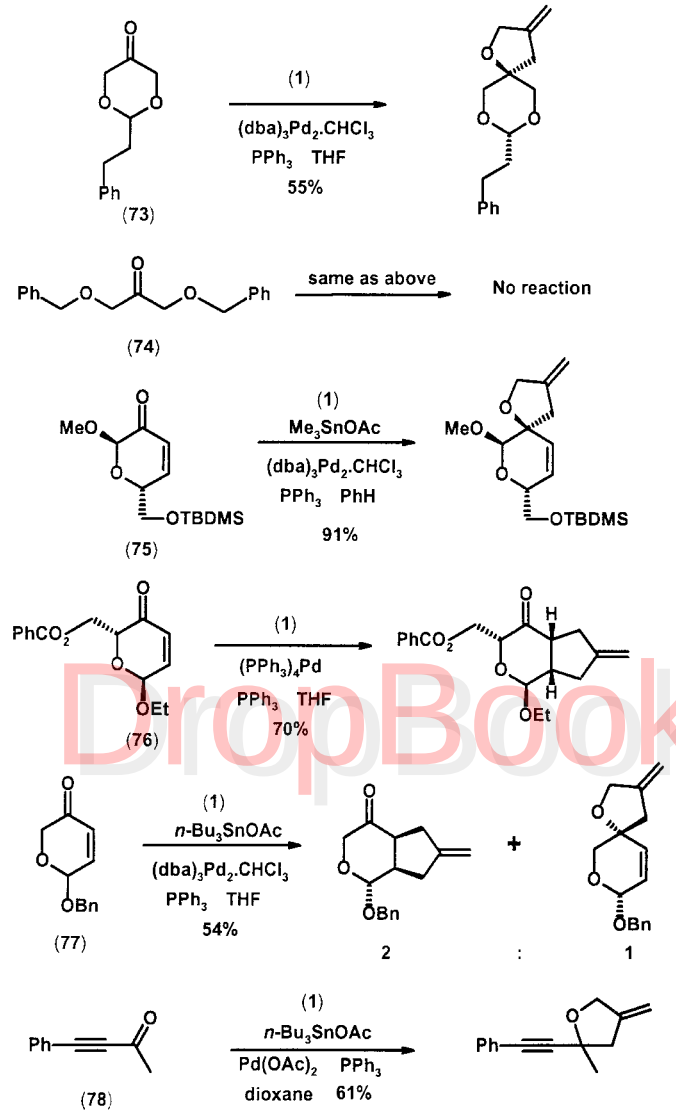
Scheme 2.21 Tin effect in substituted TMM cycloadditions with aldehydes

2.4.7
Imine Cycloadditions

The acetate (**1**) and its mosylate analog (**79**) have been shown to undergo cycloaddition with the CN double bond of alkyl imines to generate substituted pyrrolidines in the presence of nickel or palladium catalyst [35]. For example, both the phenyl imine (**80**) and the diazene (**81**) gave reasonable yields of adducts (**82**) and (**83**) respectively (Scheme 2.23).

Imines with an electron-withdrawing group at the nitrogen atom are excellent acceptors for the acetate (**1**) or the carbonate (**13**) [36]. Thus, *N*-tosylimines (**84**) gave very good yields of pyrrolidines (**85**) under typical conditions. The strained cyclic imine (**86**) and α,β-unsaturated imine (**87**) both participated smoothly in the cycloadditions. The hindered nitrimine (**88**) also reacts well with (**1**) (but not with **13**) to produce the pyrrolidine (**89**) with a 17 : 1 diastereoselectivity. However, the unhindered nitrimines from cyclohexanone and 2-nonanone failed to react presumably due to enolization (Scheme 2.24).

Placing an electron-withdrawing group on the carbon atom of the imine also increases its reactivity toward TMM cycloaddition. Glyoxalate imine (**90**, R = H) and



Scheme 2.22 TMM [3+2] cycloadditions with ketones

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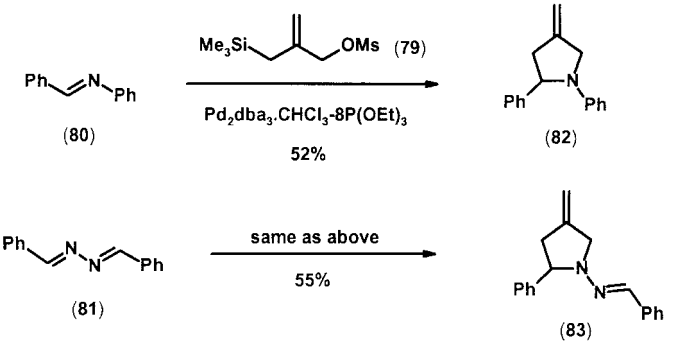
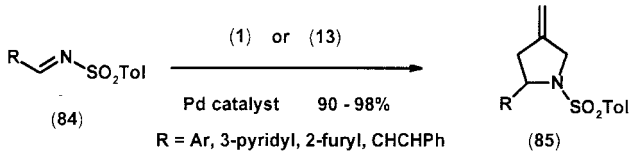
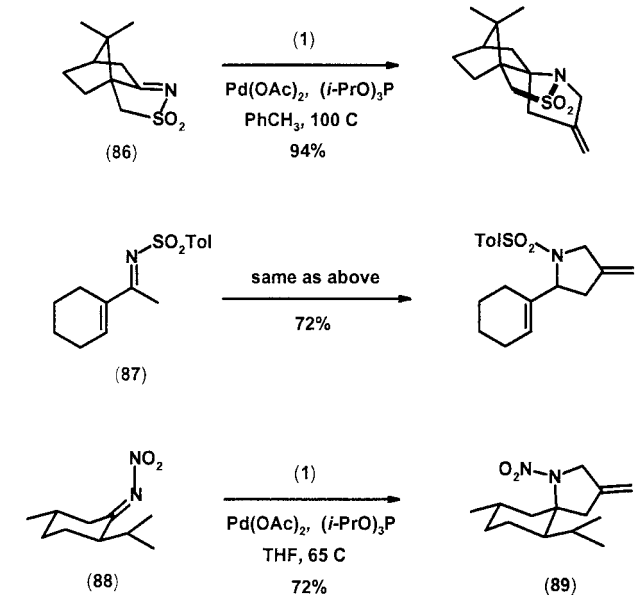
ketomalonate imine (**90**, R = CO_2Me) both formed cycloadducts in good yields, but the cyclic pyruvate imine (**91**) still required elevated temperature for reaction (Scheme 2.25) [36].

Substituted TMMs also participate smoothly in imine cycloaddition to generate more structurally elaborate pyrrolidines. The regioselectivity of these reactions is similar to that of olefin addition, although subsequent isomerization of the initial adduct is often observed. For example, the cyano system produced the thermody-

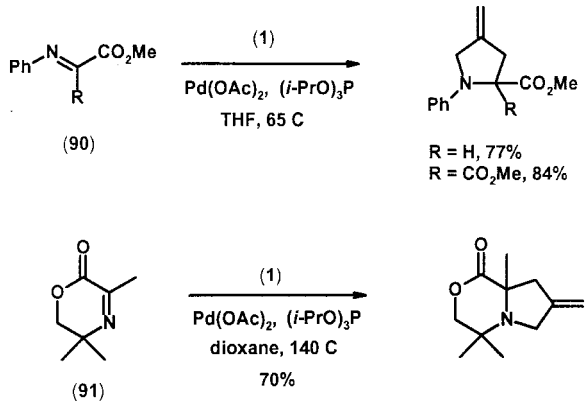


Scheme 2.23 TMM [3+2] cycloadditions with imines





Scheme 2.24 TMM [3+2] cycloadditions with N-activated imines



Scheme 2.25 TMM [3+2] cycloadditions with C-activated imines

namically more stable endocyclic conjugated isomer (**92**) [36]. A sulfide shift also accompanied the cycloaddition of imine (**93**) with the thio-substituted TMM analog to produce (**94**) as the major product. This allyl sulfide can serve as precursor to a pyrrole synthesis (Scheme 2.26) [20].

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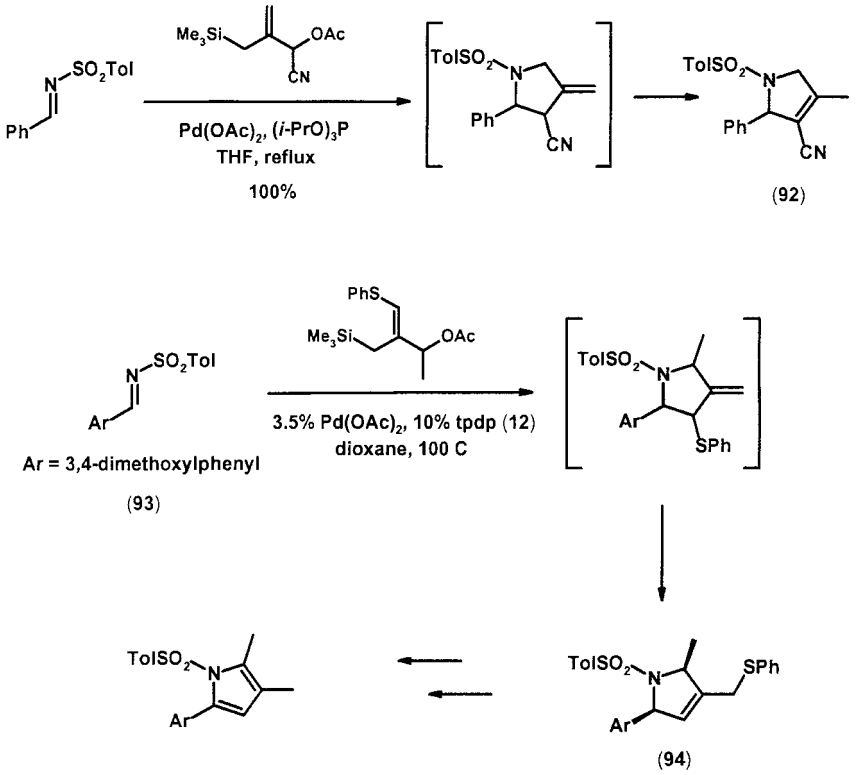
2.4.8 [4+3] Cycloadditions

TMM-Pd cycloaddition with electron-deficient 1,3-dienes provides a potentially facile route to seven-membered ring systems if the competing formation of five-membered ring products can be adequately suppressed. The stepwise mechanism of Michael addition followed by ring-closure is also believed to be operative in this case. Treatment of dimethyl (*E,E*)-muconate with (**1**) in the presence of a Pd^0 catalyst has been shown to give a mixture of methylenecycloheptene (**95**) and methylenecyclopentane (**96**), with the latter being the predominant product under typical conditions (Scheme 2.27). The use of lower reaction temperature and triisopropyl phosphite as the ligand increases the amount of seven-membered ring formation to about even with the five-membered ring product. Interestingly, a phenyl-substituted TMM yielded only the five-membered ring adduct in the reactions with the same muconate and the corresponding (*E,Z*) isomer [37].

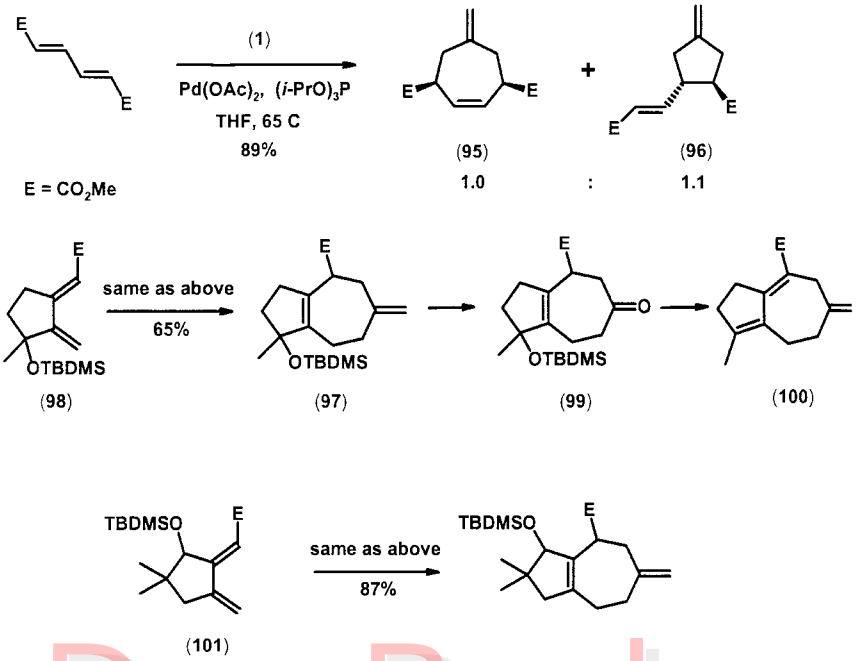
Geometrically restricting the diene to a *cisoid* conformation greatly enhances the formation of the seven-membered ring. The cycloheptene (**97**) could be obtained in 65% yield (along with 8% of the spiro-methylenecyclopentane) from the diene (**98**). Further selective elaboration of (**97**) demonstrates the versatility of this approach, as the ketone (**99**) and the dienone (**100**) can be envisioned as intermediates toward the synthesis of procurcumenol and helispendiolide, respectively. The less sterically hindered diene ester (**101**) gave exclusively the seven-membered ring adduct as a mixture of diastereoisomers (Scheme 2.27) [38].



Scheme 2.26 Substituted TMM [3+2] cycloadditions with imines

Pyrones also serve as geometrically constrained 4π-electron substrates. The parent and alkyl- and aryl-substituted pyrones undergo only [4+3] cycloaddition. The bicyclic pyrones (**102**) give rise to bridged tricyclic adducts in excellent yields. However, ester substitution on pyrone, such as the case in (**103**), tends to increase the amount of methylenecyclopentane formation [39]. A thio-substituted TMM analog reacts with the pyrone (**104**) to produce bridged product (**105**) in good yield (Scheme 2.28) [20]. The pyrone cycloadducts are very useful synthetically. The endocyclic olefin is available for further stereocontrolled elaboration. The lactone bridge represents a *cis*-1,4-substitution of carbon and oxygen, and a thermal elimination of CO_2 can lead to the formation of a cycloheptadiene.

The TMM [4+3] cycloaddition to pyrone has been employed in a synthetic study of a novel biologically active diterpene pseudolaric acid B (**106**), in which the formation of the bridged adduct (**107**) from the 2-pyrone (**108**) is the key step in the sequence (Scheme 2.29). A mixture of the other isomer (**109**) and the methylenecyclopentane (**110**) was also isolated from the reaction. It is important to point out that the presence of a tin co-catalyst is critical in effecting the reaction. This is the first example a "tin-effect" observed in a [4+3] cycloaddition [40].



Scheme 2.27 TMM [4+3] cycloadditions with 1,3-dienes

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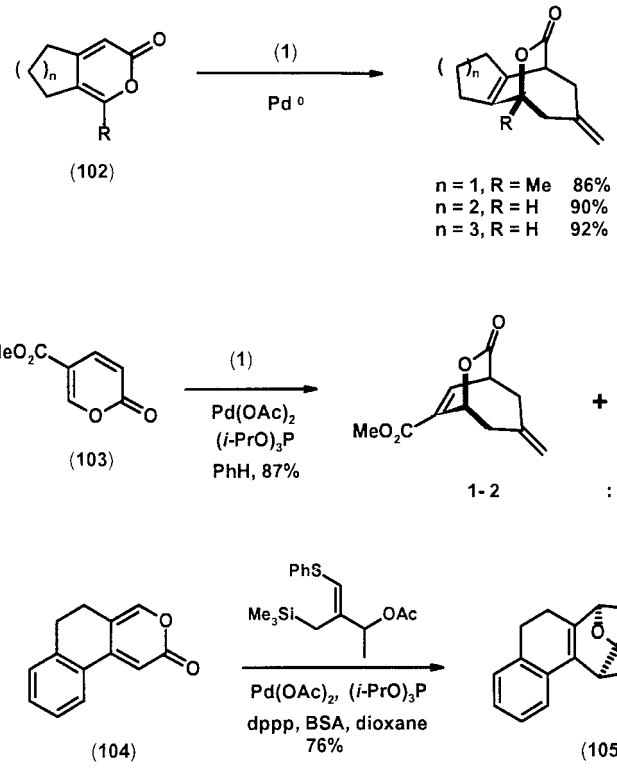
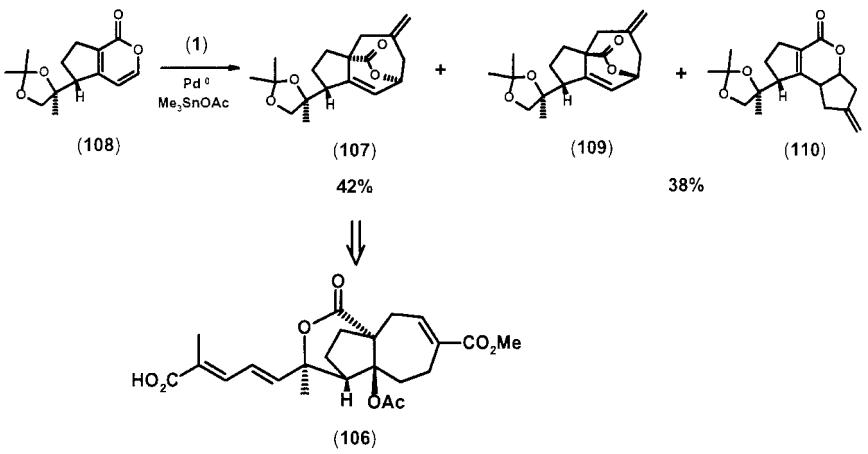
[3+2] cycloaddition tends to interfere more with the [4+3] cycloaddition when the diene acceptor is not restricted in the *cisoid* form. The Pd-catalyzed reaction of vinylcyclopentenes (**111**) with the parent TMM gave both five- and seven-membered ring adducts with ratio depending on the steric nature of the substrate. While the ketone (**111**, X=O) yielded only a [3+2] adduct, derivatization of the carbonyl with bulky ketal substituents does serve to enhance seven-membered ring formation, presumably because of a combination of both steric and electronic effect (Scheme 2.30) [41]. In contrast to the pyrone system, addition of Me_3SnOAc does not seem to impact the ratio of the cycloaddition products except for some rate enhancement [42].

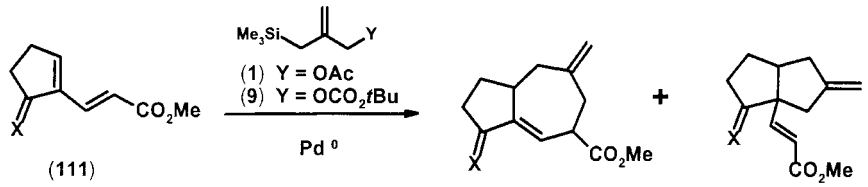
The [4+3] cycloaddition has also been realized in acceptors containing a nitrogen atom. While *α,β*-unsaturated aldimines, and structurally flexible ketimine such as (**87**), generally only undergo [3+2] cycloadditions (see Scheme 24), the ketimine (**112**), which is rigidly held in a *cisoid* conformation, does give exclusively the [4+3] adduct azepine (**113**). On the other hand, the steroidal imine (**114**) produces a quantitative yield of a 1:1 mixture of the [4+3] and [3+2] cycloadducts (**115**) and (**116**), respectively (Scheme 2.31) [36].



Scheme 2.28 TMM [4+2] cycloadditions with pyrones

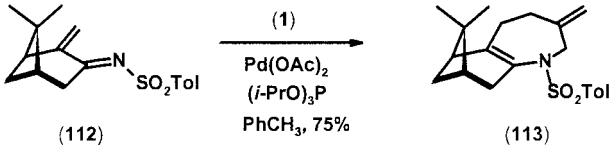


Scheme 2.29 TMM [4+3] cycloadditions in the synthetic study of pseudolaric acid B (**106**)



X = O, (1)	0%	69%
X = -OCH_2CH_2O- , (9)	39%	48%
X = -$OCH_2CMe_2CH_2O$- , (9)	48%	33%

Scheme 2.30 TMM [4+3] cycloadditions with structurally flexible 1,3-dienes



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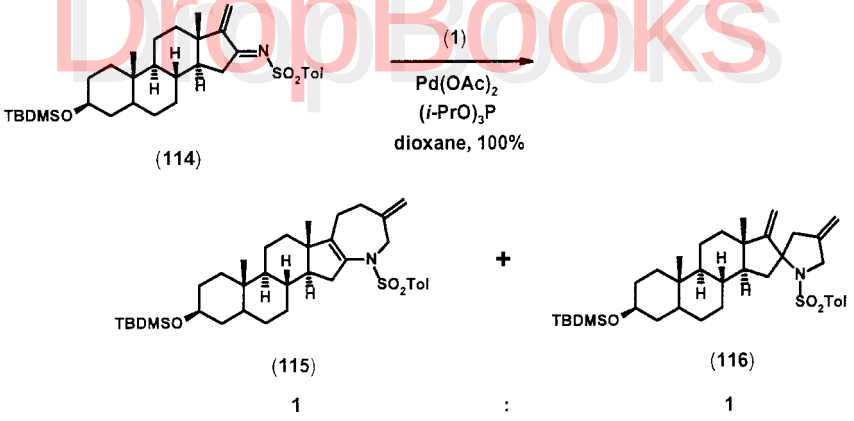
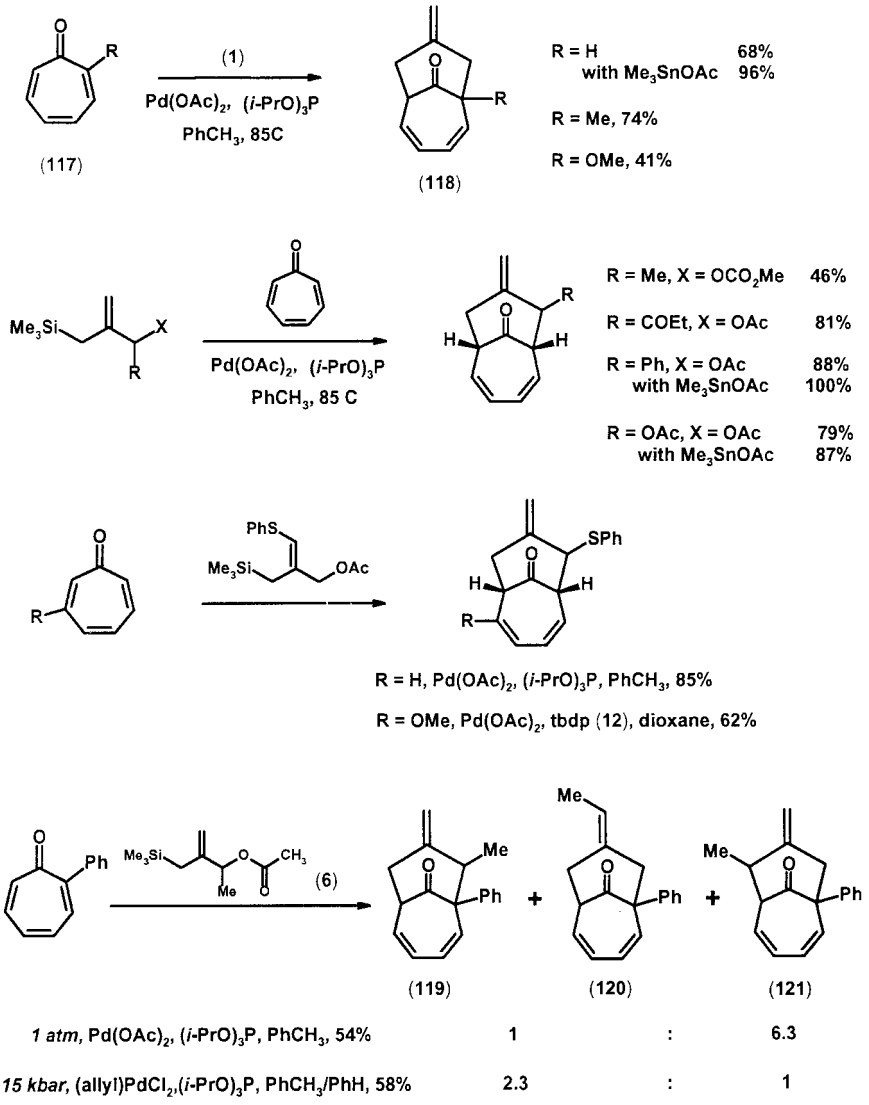


Scheme 2.31 TMM [4+3] cycloadditions with aza-1,3-dienes

2.4.9
[6+3] Cycloadditions

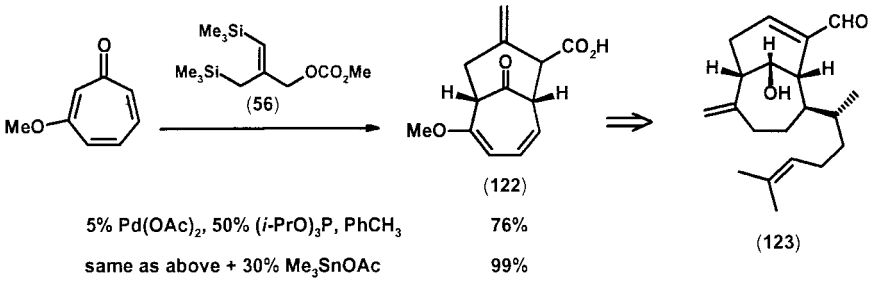
Nine-membered ring systems are potentially accessible via a TMM cycloaddition with conjugated trienes in a [6+3] fashion. However, tropone is the only reported system that undergoes such a reaction. Interestingly, these cycloadditions are remarkably selective in that only nine-membered ring products are formed,

although [3+2] and [4+3] modes of cycloaddition are also possible (Scheme 2.32). The parent TMM precursor (**1**) reacts with tropones (**117**) to give reasonable yields of the bridged [4.3.1]decanones (**118**) [43]. Various substituted TMMs also cycloadd to tropone with regioselectivity similar to that of the corresponding [3+2] cases [20, 43]. Addition of Me_3SnOAc as a co-catalyst also leads to yield improvement [16]. In the case of a phenyl-substituted tropone and a methyl-TMM, performing the reaction under high pressure favors the formation of kinetic products (**119**) and (**120**) over the thermodynamic product (**121**) [11].



Scheme 2.32 TMM [6+3] cycloadditions with tropones

Carboxylative TMM cycloaddition has also been realized with 3-methoxytropone and precursor (**56**) to produce an epimeric mixture of acids (**122**), which was employed in a synthetic study of the bicyclic diterpene sanadaol (**123**). The use of bidentate ligand tpdp (**12**) and high pressure did not improve the reaction. However, the addition of Me_3SnOAc as a co-catalyst did produce a better yield of (**122**) (Scheme 2.33) [16].



Scheme 2.33 Carboxylative TMM [4+3] cycloadditions with tropone in the synthetic study of sanadaol (**123**)

2.4.10
[3+3] Cycloaddition

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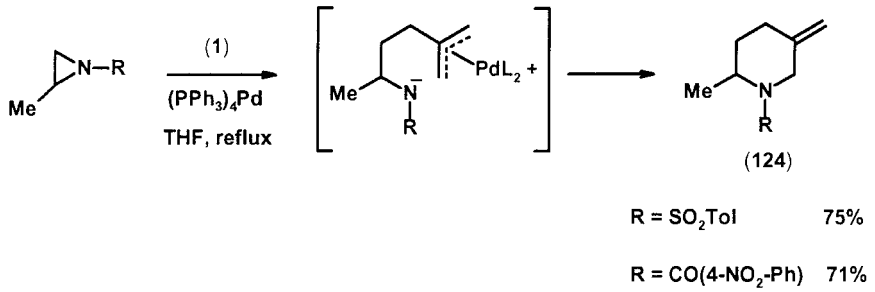
There is only one report in the literature of a [3+3] cycloaddition involving TMM and activated aziridines to give the corresponding piperidine (**124**) [44]. The formation of the six-membered ring adduct is presumed to proceed via the ring-opening of the aziridine by the attack of TMM complex (**2**) on the least hindered carbon, which is then followed by an intramolecular cyclization (Scheme 2.34).



Scheme 2.34 TMM [3+3] cycloaddition with aziridines

2.5 Conclusions

The chemistry of palladium-catalyzed TMM cycloadditions has indeed come a long way since its invention. The effort of Trost and others has succeeded in transforming a laboratory curiosity into a most powerful synthetic method. This versatile methodology has steadily gained in popularity over the years in the synthetic community in the area of cyclopentanoid construction. As presented in this review, much progress has been made in expanding the scope and fine-tuning the chemistry. Factors, such as the acyl and tin effects and high pressure, to control the reactivity and selectivity have been discovered. Seven- and nine-membered rings are now also accessible with this chemistry. With these new developments, TMM cycloadditions are becoming standard tools in five- and possibly larger membered ring construction, much like the Diels-Alder reaction in six-membered ring synthesis.

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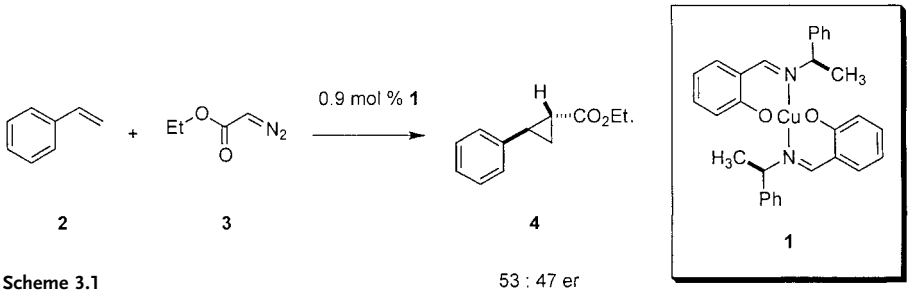
3
Enantioselective [2+1] Cycloaddition: Cyclopropanation with Zinc Carbenoids

Scott E. Denmark and Gregory Beutner

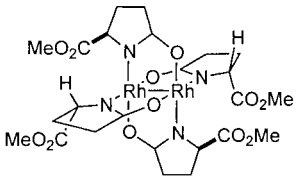
3.1 Introduction

Catalytic, enantioselective cyclopropanation enjoys the unique distinction of being the first example of asymmetric catalysis with a transition metal complex. The landmark 1966 report by Nozaki et al. [1] of decomposition of ethyl diazoacetate **3** with a chiral copper (II) salicylamine complex **1** (Scheme 3.1) in the presence of styrene gave birth to a field of endeavor which still today represents one of the major enterprises in chemistry. In view of the enormous growth in the field of asymmetric catalysis over the past four decades, it is somewhat ironic that significant advances in cyclopropanation have only emerged in the past ten years.



Scheme 3.1

From a historical perspective it is interesting to note that the Nozaki experiment was, in fact, a mechanistic probe to establish the intermediacy of a copper carbenoid complex rather than an attempt to make enantiopure compounds for synthetic purposes. To achieve synthetically useful selectivities would require an extensive exploration of metals, ligands and reaction conditions along with a deeper understanding of the reaction mechanism. Modern methods for asymmetric cyclopropanation now encompass the use of countless metal complexes [2], but for the most part, the importance of diazoacetates as the carbenoid precursors still dominates the design of new catalytic systems. Highly effective catalysts developed in



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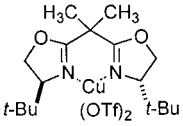

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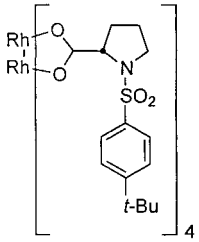

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Fig. 3.1 Cyclopropanation catalysts employing diazoacetate precursors

the laboratories of Doyle (**5**) [3a,b], Evans (**6**) [3c] and Davies (**7**) [3d,e] have shown that diazoacetates can serve as versatile precursors in highly enantio- and diastereoselective cyclopropanations (Fig. 3.1).

Whereas the utility of these methods has been amply documented, they are limited in the structures they can provide because of their dependence on the diazoacetate functionality and its unique chemical properties. Transfer of a simple, unsubstituted methylene would allow access to a more general subset of chiral cyclopropanes. However, attempts to utilize simple diazo compounds, such as diazomethane, have never approached the high selectivities observed with the related diazoacetates (Scheme 3.2) [4]. Traditional strategies involving rhodium [3a,c], copper [3b, 5] and palladium have yet to provide a solution to this synthetic problem. The most promising results to date involve the use of zinc carbenoids albeit with selectivities less than those obtained using the diazoacetates.

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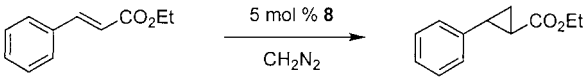

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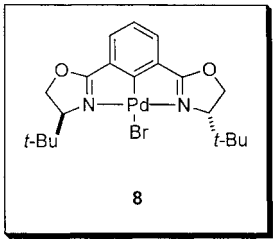

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Scheme 3.2

This review outlines developments in zinc-mediated cyclopropanation from the initial reports in the 1950s through to the current state of the art methods. The presentation will rely heavily on how the evolution of mechanistic understanding aided in the rationalization and optimization of each new advance in the asymmetric process.

The most logical starting point is a discussion of the structure of the zinc carbenoid, followed by a somewhat chronological presentation of major advances in the use of zinc carbenoids in cyclopropanation. After a brief historical recounting of Simmons and Smith's original studies, the crucial implications of diastereose-

lective, substrate-directed reactions will be discussed. The main body of the review involves the examination of the various types of enantioselective processes. Stereocontrol in Simmons-Smith cyclopropanations has been achieved by a number of strategies and these will be presented in the progression of:

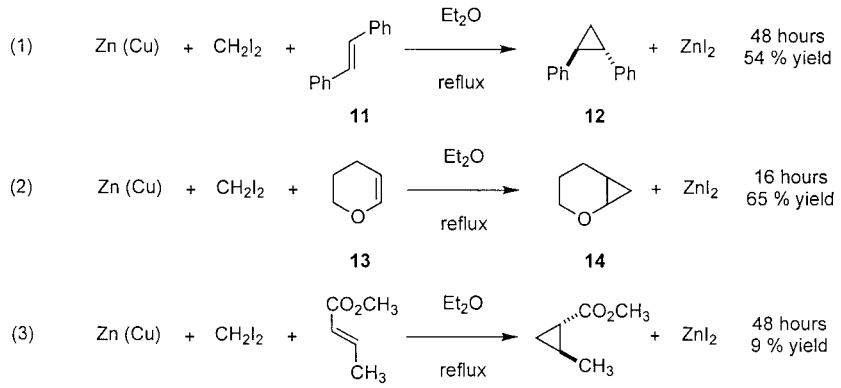
(i) auxiliary-based methods;
(ii) chirally-modified reagents; and
(iii) chiral, catalytic processes.

The discussion of the catalytic, asymmetric variants will incorporate a significant emphasis on the interplay of mechanistic investigations and synthetic optimization studies to provide a unified picture of the cyclopropanation methods. Finally, recent insights provided by computational analysis of the transition structures for cyclopropanation will be discussed.

The primary objective of this review is to provide an integrated analysis of the contributions from structural, mechanistic and preparative studies toward the successful development of a modern, stereoselective reaction. The synthetic aspects of this useful transformation have been extensively reviewed elsewhere [6].

3.2
The Simmons-Smith Cyclopropanation – Historical Background

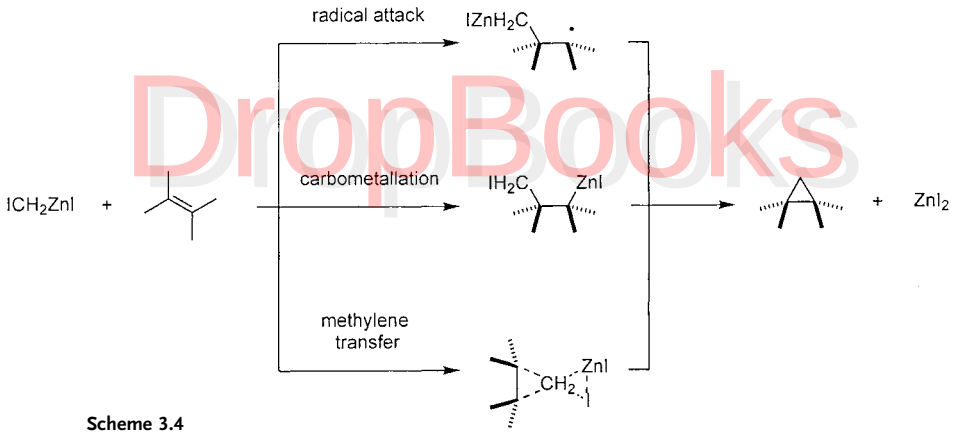
Without question, the most powerful method for cyclopropane formation by methylene transfer is the well-known Simmons-Smith reaction [6]. In 1958, Simmons and Smith reported that the action of a zinc–copper couple on diiodomethane generates a species that can transform a wide variety of alkenes into the corresponding cyclopropanes (Scheme 3.3) [7].



Scheme 3.3

The chemoselectivity of this reagent is surprising when compared to free methylene, which Doering characterized as "one of the most indiscriminate reagents" [8]. No C–H insertion products, which are common to reactions involving free carbenes, are observed. The stereospecificity of the addition is remarkable and distinct from that of free carbenes. In the cyclopropanation of *trans*-stilbene **11** (Scheme 3.3, Eq. 1), only the *trans* cyclopropane **12** is observed. On the basis of such observations, the zinc carbenoid iodomethylzinc iodide ($IZnCH_2I$), is thought to transfer a methylene unit to the alkene in a concerted manner. Simmons and Smith also proposed that the zinc carbenoid is an electrophilic reagent. When comparing the cyclopropanation of the vinyl ether **13** with that of the crotonate **15** (Scheme 3.3, Eqs 2 and 3), it was clear that the nucleophilic double bond of the vinyl ether **13** was a much more reactive partner for the zinc carbenoid.

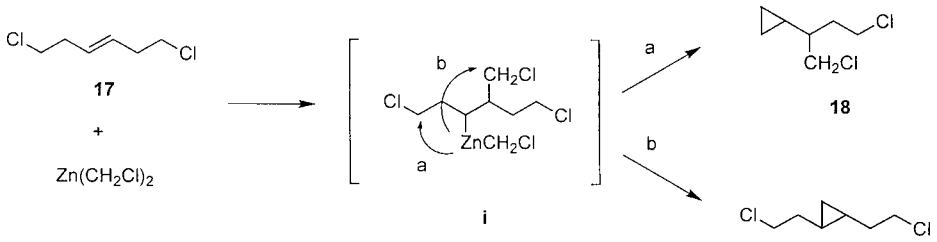
The stereospecificity of the methylene transfer provides compelling support for a concerted mechanism and this conclusion has rarely been disputed. It is instructive, however, to review the experimental evidence that allowed for the elimination of the alternative mechanistic proposals, namely, a radical addition and a carbometallation (Scheme 3.4).



Scheme 3.4

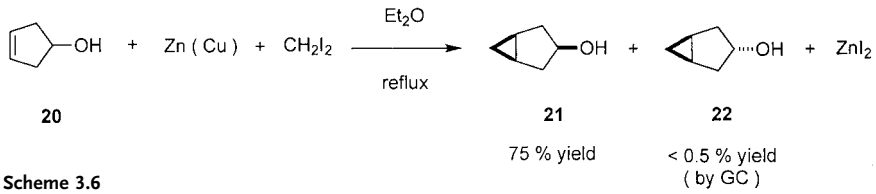
The radical addition can be directly ruled out on the basis of the high chemo- and stereoselectivity which is the hallmark of the Simmons-Smith reaction. The carbometallation mechanism is more difficult to rule out a priori because it is conceivable that high stereospecificity is possible. However, nucleophilic attack of the carbenoid on the alkene is inconsistent with reactivity patterns of the cyclopropanating reagent. Simmons and Smith repeatedly observed that electron-rich olefins were the best substrates for the reaction. Alkenes, which were conjugated to electron withdrawing groups such as esters, reacted slowly, which suggested that the carbenoid is an electrophilic species. Interestingly, Hoberg independently proposed a similar carbometallation mechanism for the cyclopropanation of alkenes with aluminum carbenoids [9]. Ultimately, Wittig provided conclusive evidence against a carbometallation path-

way [10]. In an ingenious experiment, Wittig subjected dihaloalkene **17** to the cyclopropanation conditions to differentiate the two pathways (Scheme 3.5). If carbometallation were operative, the initially formed organozinc species **i** would have two pathways (a and b) available for collapse to product. If both the terminal cyclopropane **18** and the internal cyclopropane **19** are observed, one would have to accept the intermediacy of **i** and thence, the carbometallation mechanism. If direct methylene transfer occurs, only the internal cyclopropane **18** will be formed. Wittig found only the dialkylcyclopropane product **18** expected from direct methylene transfer. Clearly, the original proposal of a concerted mechanism is consistent with the experimental observations. Moreover, all computational analyses of the fundamental process (see Section 3.5) favor reaction surfaces with a single transition state between the starting alkene and the resulting cyclopropane.



Scheme 3.5

This method was enthusiastically adopted by synthetic chemists and within a few years, it had greatly expanded in scope [6]. Clearly, the lack of structural information or a detailed understanding of reaction mechanism did not hamper the rapid application of this reaction in various endeavors. In the course of one of these early applications, Winstein et al. made a startling observation that would be crucial to the understanding and future development of asymmetric processes. In attempting to improve the synthesis of bicyclo[3.1.0]hexen-3-ol **21**, they noted the dramatic effect of a neighboring hydroxyl group on the rate and stereochemical course of the cyclopropanation (Scheme 3.6) [11]. The importance of this observation was not lost on Winstein or many others (vide infra) who capitalized on this powerful effect to further enhance the synthetic potential of the reaction [12]. However, the implications of this behavior for the development of asymmetric cyclopropanations and the insight it provided on the structure of the reagents were



Scheme 3.6

not appreciated until much later [13]. In passing, it is interesting to note that this stands as one of the earliest examples of a substrate-directed reaction [14].

These early studies on zinc carbenoids provide an excellent foundation for the development of an asymmetric process. The subsequent appearance of chiral auxiliary and reagent-based methods for the selective formation of cyclopropanes was an outgrowth of a clear understanding of the achiral process. However, the next important stage in the development of catalytic enantioselective cyclopropanations was elucidation of the structure of the Simmons-Smith reagent.

3.3
Structure and Dynamic Behavior of Zinc Carbenoids

3.3.1
Formation and Analysis of Zinc Carbenoids

A prerequisite for a fundamental understanding of any reaction is the knowledge of the constitution and structure of the reagents. Such insight is useful for predicting and rationalizing both reactivity and selectivity. With regard to the Simmons-Smith cyclopropanation, reliable structural data for the zinc carbenoids did not appear until quite recently because of the many experimental difficulties associated with the study of these transient, highly reactive organometallic species. Further complications introduced by chemical exchange phenomena (Schlenk equilibrium) and solvation state changes may render definitive interpretation difficult. Fortunately, crystallographic and spectroscopic analysis of carefully prepared samples has lent some clarity to this complex problem.

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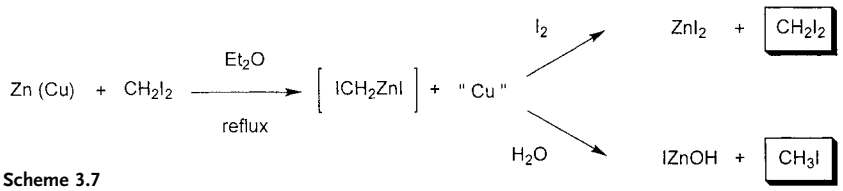
One of the major challenges in formulating a unified picture of zinc carbenoid structure is the variety of methods employed for their preparation [6f]. Each method has distinct advantages in terms of synthetic utility and in application to asymmetric catalysis. From the extensive literature on this subject, three major classes of preparative methods can be identified. The first method involves combination of a zinc-metal couple with a dihalomethane in diethyl ether as pioneered by Emschwiller. In 1929, Emschwiller reported the preparation of what he assigned as $IZnCH_2I$ on the basis of chemical characterization by hydrolysis and iodolysis (Scheme 3.7) [15]. The use of an active metal couple has remained a popular method for generation of zinc carbenoids and was the method of choice used by Simmons and Smith in their studies [7]. The reliable and reproducible genera-

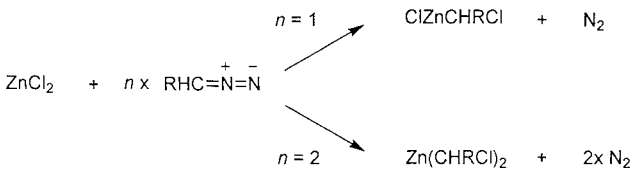


Scheme 3.7

tion of an active metal couple represented a preparative challenge that has resulted in a number of recipes for the Simmons-Smith reagent [16].

Despite its utility in synthetic applications, this method is rarely used for asymmetric catalysis. A significant drawback of this process is the heterogeneity of the reagent. Although it has been shown that filtration of the suspension does not lead to a decrease in activity, the presence of a solid is an undesirable complicating factor for a catalytic system [17]. The requirement for an ethereal solvent may also cause problems by introducing a large number of Lewis basic molecules which can compete with a chiral ligand for binding of the Lewis acidic zinc atom, leading to a substantial contribution from an achiral pathway.

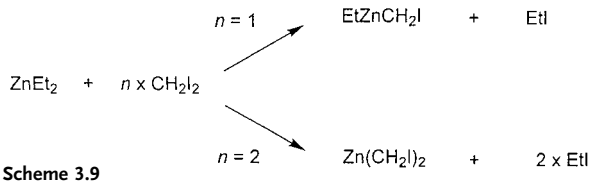
A second general method for the preparation of zinc carbenoids involves two different precursors (Scheme 3.8). In 1960, Wittig demonstrated that a number of main group and late transition metal halides could be converted to carbenoids in the presence of diazomethane [10, 18]. Zinc salts were particularly useful in this process since they minimized the unproductive formation of polymethylene. These studies also introduced a new type of zinc carbenoid. From hydrolysis studies, Wittig concluded that he could selectively introduce either one or two methylene units to form chloromethylzinc chloride, $ClCH_2ZnCl$, or bis(chloromethyl)zinc, $Zn(CH_2Cl)_2$. This method has the added advantage of facile introduction of functionalized carbene units through the use of substituted diazo compounds [19]. However, a major drawback of this method for asymmetric catalysis is the difficulty of preparing anhydrous diazomethane [20] since moisture can lead to decomposition of the resulting carbenoid species.



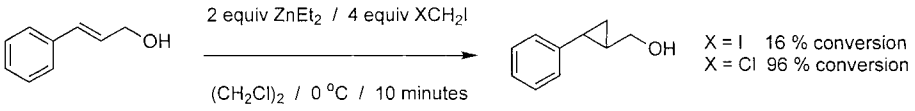
Scheme 3.8

A third preparation has become the method of choice for formation of zinc carbenoids, particularly in the field of asymmetric catalysis. In 1966, Furukawa reported that diethylzinc ($ZnEt_2$) reacts with diiodomethane to generate a zinc carbenoid by halogen metal exchange (Scheme 3.9) [21]. Much like the Wittig procedure, the exact stoichiometry of the reagents is easily controlled since both precursors can be accurately metered as liquids. On the basis of the reagent stoichiometry (and subsequent spectroscopic and crystallographic studies), the procedure can generate either ethyl iodomethylzinc ($EtZnCH_2I$) or bis(iodomethyl)zinc ($Zn(CH_2I)_2$). In addition, the reagents can be prepared at low temperature and in non-coordinating solvents, a distinct advantage for potential catalytic systems. The original Furukawa procedure has been elaborated to include the use of alternative carbenoid sources such as chloroiodomethane. For example, Denmark et al. have documented the increased reactivity of $Zn(CH_2Cl)_2$ relative to $Zn(CH_2I)_2$ (Scheme

3.10) [22]. Interestingly, this more reactive reagent does not lend itself to use in asymmetric protocols. As will be shown later, reactions run using $Zn(CH_2Cl)_2$ are far less selective than those employing $Zn(CH_2I)_2$. In addition, the selective formation of $EtZnCH_2I$ has also allowed for the generation of a more reactive agent, presumed to be $CF_3CO_2ZnCH_2I$ by protonolysis of the ethyl group with trifluoroacetic acid [23].



Scheme 3.9



23 **24**

Scheme 3.10

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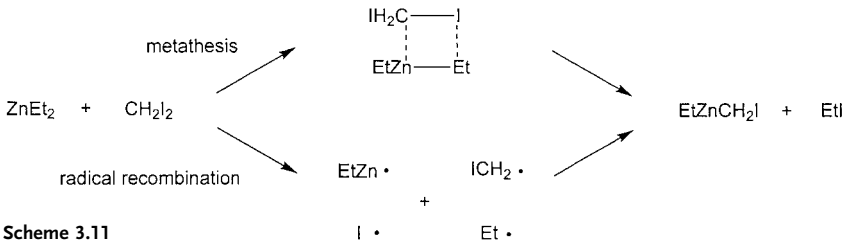
In contrast to the extensive body of work on the preparation of these zinc carbenoids, few investigations are on record concerning the mechanism of the Furukawa method for carbenoid formation. Two limiting mechanisms can be envisioned – a concerted metathesis via a four-centered transition structure or a stepwise radical cleavage-recombination (Scheme 3.11).



Scheme 3.11

The possibility of a radical mechanism is supported by the observation of the accelerating effect of molecular oxygen on the cyclopropanation. Miyano et al. discovered that the addition of dioxygen accelerated the formation of the zinc carbenoid in the Furukawa procedure [24a, b]. The rate of this process was monitored by changes in the concentration of ethyl iodide, the by-product of reagent formation. Comparison of the reaction rate in the presence of oxygen with that in the

Tab. 3.1 Rate enhancements in the presence of radical initiators

Entry	*Additive*	*Reaction*		*Yield (%)*
		Time (h)	*Temp. (°C)*	
1	None	7	70	4
2	Oxygen	1.5	50	70
3	AIBN	2	70	46
4	UV light	1.5	23	73

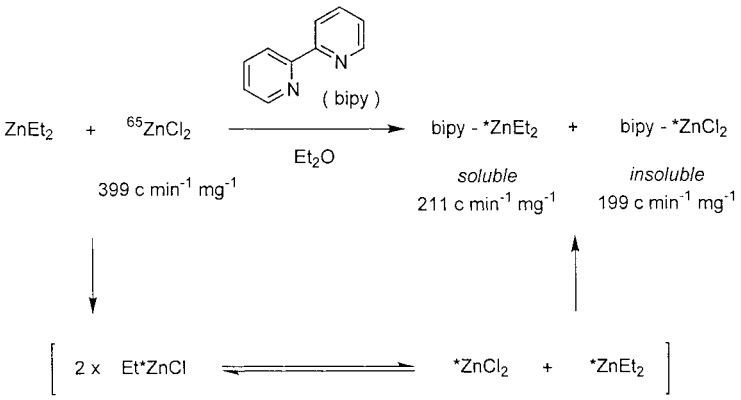
presence of AIBN or UV light shows similar rates enhancements, again suggesting the importance of the radical pathway (Table 3.1). In view of the well-established effect of molecular oxygen on the rate of cleavage of carbon-boron bonds, the similar behavior with zinc does not seem unreasonable [25].

Early studies on the composition of zinc carbenoids relied on chemical analysis of gaseous products formed upon hydrolysis [15, 17, 18]. Indeed, many of the conclusions drawn by Smith and Wittig relied upon a combination of hydrolytic decomposition and iodometric titrations. Although this kind of analysis may be sufficient for gross reagent composition, little structural information can be gleaned from this data. It was, moreover, well known that zinc carbenoids are dynamic species which undergo rapid ligand exchange in accordance with the Schlenk equilibrium. Thus, the results of chemical analysis give an overall average composition of all species present, which clearly is an incomplete picture.

3.3.2
Studies on the Schlenk Equilibrium for Zinc Carbenoids

The study of the Schlenk equilibrium for organozinc compounds represents a major chapter in the understanding of these reagents in general [26]. Before elaborating the studies on zinc carbenoids, it is appropriate to briefly review the definitive investigations on organozinc halides themselves.

One of the earliest studies involved the use of radiolabelled ^{65}Zn species. In 1963, Dessy and Coe attempted to establish if a Schlenk equilibrium were operative by analyzing the isotopic composition of diethylzinc after exposure to labeled zinc chloride, $ZnCl_2$ (Scheme 3.12) [27]. Thus, $^{65}ZnCl_2$ and $ZnEt_2$ were combined and the residual $ZnCl_2$ was separated out by precipitation with 2,2′-bipyridyl. The remaining $ZnEt_2$ was found to contain some of the radiolabel introduced in the zinc chloride. The labeled $^{65}ZnCl_2$ had an initial value of 399 c min^{-1} mg^{-1} after combustion to zinc oxide. The $ZnCl_2$ recovered from the experiment was shown to have a count of 199 c min^{-1} mg^{-1}. This statistical distribution of the radiolabel provided clear evidence for the existence of the Schlenk equilibrium. However, these results provided no information on the position of this equilibrium or the effect of solvents and additives on the relative populations of the two zinc species. Answers to these questions would require a different kind of analysis.



Scheme 3.12

The application of modern analytical techniques such as infrared (IR) and nuclear magnetic resonance (NMR) spectroscopy have allowed for considerable advances in the study of organozinc compounds [28]. Early studies based on chemical and molecular weight analysis by Abraham and Hill regarding the behavior of mixtures of diethylzinc and zinc iodide in tetrahydrofuran (THF) suggested that the Schlenk equilibrium lay strongly on the side of the mixed organozinc species, ethylzinc iodide (CH_3CH_2ZnI) [29]. Later work by Evans et al. confirmed this conclusion with a careful IR study of these THF-solvated organozinc compounds [28e]. Upon mixing equimolar amounts of diethylzinc and zinc iodide, the characteristic $\nu_{as}(Zn–CH_2)$ stretch of diethylzinc at 534 cm^{-1} vanishes completely. In its place, a strong absorption appears at 510 cm^{-1}, corresponding to the $\nu(Zn–CH_2)$ for ethylzinc iodide. This rapid and complete change in the IR absorption of this mixture strongly supports the fact that in coordinating solvents, this Schlenk equilibrium strongly favors the mixed organozinc species, CH_3CH_2ZnI.

The effect of solvent on this Schlenk equilibrium is demonstrated in a subsequent ^1H NMR study. Boersma et al. investigated the Schlenk equilibrium of ethylzinc halides in toluene using ^1H NMR spectroscopy (Fig. 3.2) [28d]. Since these observations were taken under rapid exchange conditions ($\tau < 0.004$ s), only one set of ^1H signals is observed. The position of these signals relative to the limiting values for CH_3CH_2ZnX (δCH_2 ~0.6 ppm) and $Zn(CH_2CH_3)_2$ (δCH_2 ~0.1 ppm) is indicative of the relative amounts of each organozinc species in solution.

For ethylzinc chloride, CH_3CH_2ZnCl, and ethylzinc bromide, CH_3CH_2ZnBr, there is a linear relationship between the observed chemical shift and the ratio of ethylzinc halide to diethylzinc. Extrapolation of these lines to $x=1$ (mol fraction of CH_3CH_2ZnX) gives predicted values for the average chemical shift that closely match those measured for these species. This indicates that for these two organozinc halides, the Schlenk equilibrium lies heavily on the side of the ethylzinc halide in toluene. However, in the case of ethylzinc iodide, CH_3CH_2ZnI, there is a

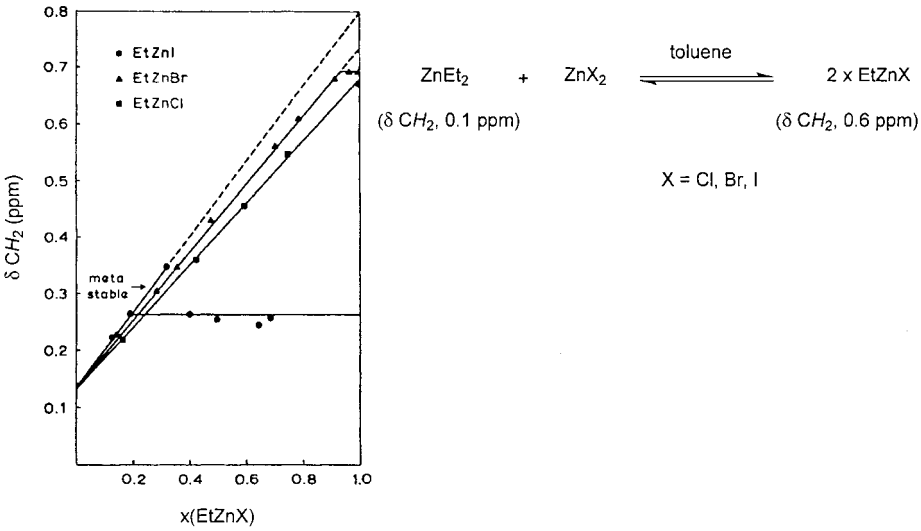
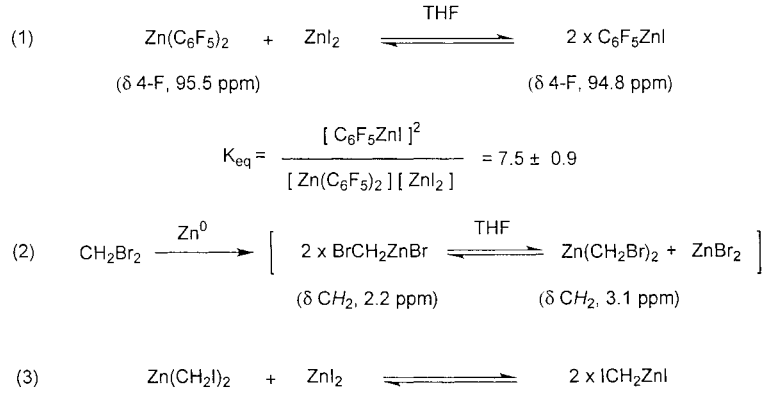


Fig. 3.2 ^{1}H NMR investigation of some organozinc halides. [Boersma, J.; Noltes, J.G. *J. Organomet. Chem.* **1267**, *8*, 551. Reprinted with permission from Elsevier, Ltd.]

constant value of the observed chemical shift at $x > 0.2$. In solutions where the ratio of CH_3CH_2ZnI to $Zn(CH_2CH_3)_2$ exceeds 0.2, rapid deposition of ZnI_2 occurs. Such a result can be expected if disproportionation of CH_3CH_2ZnI is occurring. Apparently, $Zn(CH_2CH_3)_2$ is capable of solubilizing CH_3CH_2ZnI at a given stoichiometry. The ^{1}H NMR data indicate that the equilibrium ratio of CH_3CH_2ZnI to $Zn(CH_2CH_3)_2$ is approximately 0.5 at saturation. On the basis of these observations, Boersma concludes the extent of the disproportionation reaction and hence the position of the Schlenk equilibrium is a reflection of the relative solubilities of the two organozinc species.

It is interesting to note the effect that the nature of the pendant groups has on the Schlenk equilibrium. A dramatic illustration of this comes from an ^{19}F NMR study of the position of the Schlenk equilibrium for perfluoroorganozinc reagents in coordinating solvents such as THF. By monitoring changes in the resolved signals for the *para* fluorine atoms of pentafluorophenylzinc iodide, C_6F_5ZnI ($\delta(F_p) = 95.5$ ppm), and bis(pentafluorophenyl)zinc, $Zn(C_6F_5)_2$ ($\delta(F_p) = 94.8$ ppm), valuable thermodynamic and kinetic data regarding the position and rate of establishment of the equilibrium was obtained (Scheme 3.13, Eq. 1) [28f]. After mixing equimolar amounts of $Zn(C_6F_5)_2$ and ZnI_2, the concentrations of C_6F_5ZnI and $Zn(C_6F_5)_2$ were determined by relative integration at several concentrations and temperatures. The equilibrium is found to slightly favor C_6F_5ZnI ($K_{eq} = 7.5 \pm 0.9$). This result is surprising since the corresponding THF-solvated protio system studied by Evans showed a nearly exclusive preference for the mixed organozinc [28e]. Because of the strongly electron-withdrawing nature of the pentafluorophenyl groups, the moderate position of this equilibrium may reflect the enhanced Lewis acidity of $Zn(C_6F_5)_2$. Stronger binding of Lewis basic THF molecules to this zinc



Scheme 3.13

atom may enhance its solubility relative to C_6F_5ZnI. The Arrhenius analysis of the process reveals that the redistribution is favored entropically, but is enthalpically neutral ($\Delta H = 0.88 \pm 0.30$ kJ mol^{-1} and $\Delta S = 16$ J mol^{-1} K^{-1}). The lifetime of C_6F_5ZnI is found to be 4.5×10^{-2} s at 85 °C.

The application of NMR techniques to the Schlenk equilibrium of zinc carbenoids was first reported by Fabisch and Mitchell in 1984 [30]. This study probed the existence and position of the Schlenk equilibrium for bromomethylzinc bromide in THF by ^{1}H NMR analysis (Scheme 3.13, Eq. 2). A 1:1 mixture of zinc metal and dibromomethane cleanly produces a species assigned as bromomethylzinc bromide ($BrCH_2ZnBr$) (^{1}H δCH_2 2.1–2.3 ppm). On standing for several hours, however, a new species begins to appear (^{1}H δ 3.1 ppm). In the absence of other information regarding these species, they assigned the new resonance to bis(bromomethyl)zinc ($Zn(CH_2Br)_2$). Their assignments are made by analogy to chemical shift changes in a study of mercury carbenoids by Seyferth [31]. Whereas the methylene group in $BrCH_2HgBr$ appears at 2.2 ppm, that in $Hg(CH_2Br)_2$ appears at 3.18 ppm. On the basis of the slow transformation of $BrCH_2ZnBr$ to $Zn(CH_2Br)_2$, they concluded that $Zn(CH_2Br)_2$ is the more thermodynamically stable species, but the rate of equilibration is fairly slow.

In 1992, Denmark et al. undertook a similar NMR investigation of the proposed Furukawa reagent, $Zn(CH_2I)_2$ (Scheme 3.13, Eq. 3) [32]. The isolated carbenoid was characterized by both ^{1}H and ^{13}C NMR spectroscopy. Still, with only chemical shift information, it is difficult to unambiguously assign the structures. Since it is known that ethereal solvents strongly associate with Lewis acidic zinc atoms, the possibility of isolating an ether-zinc carbenoid complex was investigated. Analysis of the spectroscopic data for such a zinc complex not only provides chemical shift information, but it provides information regarding the composition of the putative carbenoid species. Since the composition of the chelating ether ligand is known, integration can be used to unambiguously identify the structure of the carbenoid species. By adding 1,2-dimethoxyethane (DME) to solutions of diethylzinc in benzene-d_6, a DME-diethylzinc complex **25** can be formed and observed by NMR

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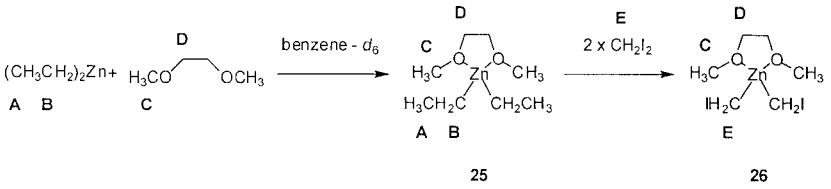
spectroscopy (Table 3.2). When two equivalents of CH_2I_2 are added to the complex **25**, a clear change in both the ^1H and ^{13}C spectra occurs. The ^1H NMR signals corresponding to the Zn–CH_2CH_3 groups are lost and a new signal, corresponding to the iodomethylzinc group, appears at 1.40 ppm. ^1H NMR integration reveals that this newly formed organozinc species **26** bears two iodomethyl groups. The chemical shift value of the methylene in the DME complex ($\delta = 1.4$ ppm) also agrees with that observed when the carbenoid is generated by a similar procedure in the absence of DME. This indicates that the ether does not affect or interfere with formation of the carbenoid. Despite its apparent role as a spectator, it does interfere with the subsequent reactivity of the carbenoid species. The complex **26** is unreactive towards alkenes, an observation which supports the notion of coordinative unsaturation as a pre-requisite for the reactivity of a zinc carbenoid. These experiments conclude that the formation of $Zn(CH_2I)_2$ is exclusive under the Furukawa conditions (2:1, $CH_2I_2/ZnEt_2$). No signals corresponding to any other zinc carbenoid are observed. Attempts to crystallize this DME-$Zn(CH_2I)_2$ complex **26** and confirm the NMR interpretation were unsuccessful.

The use of (1*S*,2*R*,3*S*)-bornanediol-derived bis ether **27** as a ligand for $Zn(CH_2I)_2$ provides important structural insights (Fig. 3.3). First, the rigidly poised, basic oxygens provide for a strongly coordinating ligand as seen in the ^1H NMR spectrum of the **27**-$Zn(CH_2I)_2$ complex **28**. Because of the chirality of the ligand, the methylene protons of the carbenoid are now diastereotopic, evidenced by their conversion from a singlet (in the DME complex) to an AB quartet. A further consequence of chelation is that two signals should be observed for each of the distinct iodomethyl groups. The two groups are no longer related by symmetry and they exist in different chemical environments. The appearance of only one AB quartet indicates that there is a rapid chemical exchange interconverting



Tab. 3.2 ^1H NMR study of the DME complex of the Furukawa reagent

Entry	*Species*	*^1H NMR (δ, ppm)*				
		A	**B**	**C**	**D**	**E**
1	CH_2I_2	–	–	–	–	2.95
2	$(CH_3CH_2)_2Zn$	1.12	0.10	–	–	–
3	$(CH_3OCH_2)_2$	–	–	3.11	3.32	–
4	**25**	1.31	0.25	3.01	3.14	–
5	**26**	–	–	3.02	2.97	1.40

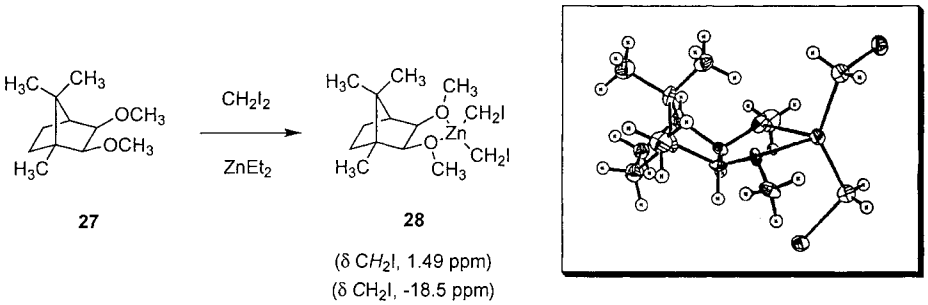


Fig. 3.3 ^{1}H NMR and X-ray crystallography study of the bis-ether complex **28**. [Denmark, S.E.; Edwards, J.P.; Wilson, S.R. *J. Am. Chem. Soc.* **1992**, *114*, 2592. Reprinted with permission from The American Chemical Society]

the two methylene groups. The two signals could not be resolved, even at low temperatures, attesting to the rapid rate of exchange.

Most importantly, this complex afforded crystals suitable for X-ray analysis. This provides the first crystallographic data regarding a zinc carbenoid. Examination of the X-ray structure confirms that the initially formed carbenoid reagent is $Zn(CH_2I)_2$ (Fig. 3.3) [33]. The crystal structure reveals several interesting features of this complex. The complex crystallizes as a monomer, although two distinct molecules are visible within one unit cell. The differences in the two structures are minor. The two iodomethyl groups are clearly distinguished in the solid state, despite their coalescence on the NMR time-scale. The upper group is in close contact with the dimethyl bridge of the ether ligand. To avoid unfavorable steric interactions, the iodine is positioned out and away from the bis-ether backbone. The lower group, which does not encounter the steric bulk of the dimethyl bridge, is rotated in an opposite orientation leaving the iodine over the zinc chelate ring. The disposition of the two iodomethyl groups around the central zinc atom is slightly bent (C–Zn–C = 138.5 °). Although such organozinc species are assumed to be linear around the zinc atom, this deviation can easily be explained by the influence of the coordinated oxygen atoms. In terms of bond lengths, the attachment of the ether ligand seems to have little effect on the gross structural features of the carbenoid. The carbon-iodine bonds are not elongated relative to a typical sp^3-carbon bound iodide (2.13–2.21 Å) [34a]. It is also interesting to note that bond lengths of the zinc-carbon bonds are equivalent to those observed in the crystal structures of other alkylzinc species (1.92–1.98 Å) [34b–e].

Although this study is a major advance in clarifying the structure of these organozinc reagents, it did not, at the time, address the Schlenk equilibrium issue. Because ZnI_2 is the sole by product of the methylene transfer process, its concentration is constantly increasing over the course of a cyclopropanation. Thus, whereas $Zn(CH_2I)_2$ may accurately describe the preformed zinc carbenoid, disproportionation with ZnI_2 formed during the reaction is a distinct possibility. Thus, it is imperative to investigate the influence of the zinc iodide, ZnI_2, on the composition of the initially formed reagent. If the ZnI_2 formed can combine with $Zn(CH_2I)_2$

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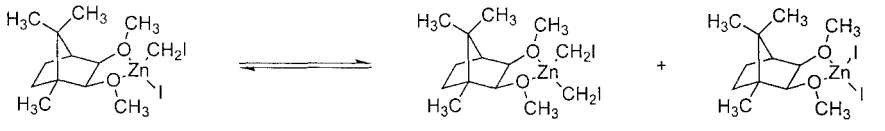
to generate the putative Simmons-Smith reagent, ICH_2ZnI, then the possibility that ICH_2ZnI is the active species throughout the cyclopropanation cannot be excluded.

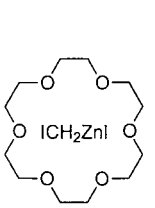
To gain information on the interconversion of all species concerned ($Zn(CH_2I)_2$, ZnI_2, and ICH_2ZnI); Charette et al. made recourse to the use of Denmark's chelating bis ether **27** to slow the exchange process and to facilitate spectroscopic identification of the species. The experimental design used by Charette et al. approached the establishment of this Schlenk equilibrium from the other side (Scheme 3.14) [35]. Formation of ICH_2ZnI in the presence of the chiral bis ether **27** leads to clean formation of the complex **29**, which is characterized by ^1H and ^{13}C NMR spectroscopy. This compound clearly differs from the complex **27**-$Zn(CH_2I)_2$ (**28**) reported by Denmark et al. Formation of the complex **27**-ZnI_2 (**30**) also leads to a unique set of signals. When the solution behavior of **29** is observed over a variety of temperatures, the related complexes **28** and **30** are never observed, suggesting that ICH_2ZnI is the thermodynamically favored species. Although **29** could not be crystallized, Charette has obtained a crystal structure of the corresponding complex of ICH_2ZnI with 18-crown-6 **31** (Fig. 3.4) [36].

This conclusion must, however, be tempered with two important caveats. Firstly the conclusion is based on a negative experiment; the lack of change of the com-



29 (δ CH_2I, -19.3 ppm) **28** (δ CH_2I, -15.1, -17.4 ppm) **30**

Scheme 3.14



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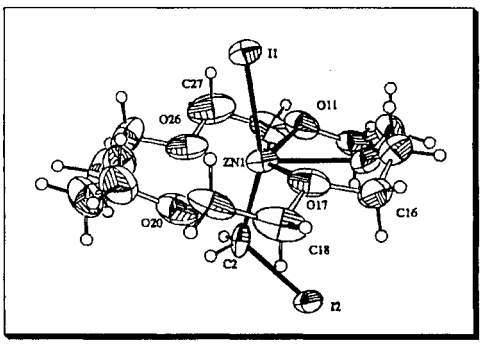

Fig. 3.4 X-ray crystal structure of the 18-crown-6-ICH_2ZnI adduct **31**. [Charette, A.B.; Marcoux, J.F.; Bélanger-Gariépy, F. *J. Am. Chem. Soc.* **1996**, *118*, 6792. Reprinted with permission from The American Chemical Society]

plex **29** could simply mean that ICH_2ZnI is inert to disproportionation while complexed. To resolve this, the equilibrium should also be approached from the other direction by combining **28** and **30**. If no equilibration occurs then unfortunately the experiment is flawed by the perturbation introduced by the need for complexing these agents. A more conclusive study on the role of the Schlenk equilibrium in course of cyclopropanation with Furukawa-type reagents was reported by Denmark and will be described in a later section on asymmetric catalysis. Thus, even though $Zn(CH_2I)_2$ is the direct product of the Furukawa preparation, its role in the cyclopropanation is probably less important than that of ICH_2ZnI.

These foregoing studies have placed the chemistry of zinc carbenoids on a more solid structural footing. The early conclusion that ICH_2ZnI was the active species formed under Simmons-Smith conditions was solely based upon titration studies, techniques unable to provide insight into rapid dynamic processes occurring in solution. With the advent of NMR spectroscopy, more in depth investigations lent clarity to this complex situation. By use of the Furukawa procedure, the initially formed species is clearly $Zn(CH_2I)_2$. However, in the presence of ZnI_2, disproportionation to ICH_2ZnI occurs. Since ZnI_2 is the inorganic byproduct of the cyclopropanation, earlier studies which assumed $Zn(CH_2I)_2$ to be the active reagent would have to be re-evaluated. Not only do these carbenoid species differ in terms of structure, they also differ in terms of reactivity and selectivity. This re-evaluation will be particularly important for understanding the role of ZnI_2 in the asymmetric variant of the cyclopropanation.

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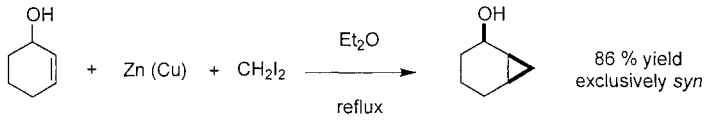
3.4 Stereoselective Simmons-Smith Cyclopropanations

3.4.1 Substrate-directed Reactions

The landmark report by Winstein et al. (Scheme 3.6) on the powerful accelerating and directing effect of a proximal hydroxyl group would become one of the most critical in the development of the Simmons-Smith cyclopropanation reactions [11]. A clear *syn* directing effect is observed, implying coordination of the reagent to the alcohol before methylene transfer. This characteristic served as the basis of subsequent developments for stereocontrolled reactions with many classes of chiral allylic cycloalkenols and indirectly for chiral auxiliaries and catalysts. A full understanding of this phenomenon would not only be informative, but it would have practical applications in the rationalization of asymmetric catalytic reactions.

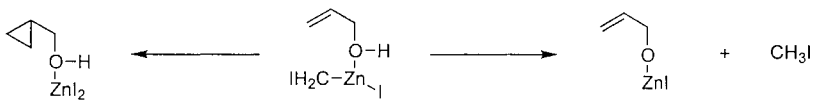
In 1963, Dauben and Berezin published the first systematic study of this *syn* directing effect (Scheme 3.15) [37]. They found that the cyclopropanation of 2-cyclohexen-1-ol **32** proceed in 63% yield to give the *syn* isomer **33** as the sole product. They observed the same high *syn* diastereoselectivity in a variety of cyclic allylic alcohols and methyl ethers. On the basis of these results, they reasonably conclude that there must be some type of coordinative interaction between the zinc carbenoid and the substrate.



32 **33**

Scheme 3.15

For free hydroxyl groups the question remained if this was a simple coordinative interaction or if the reaction was proceeding through a zinc alkoxide. The sensitivity of these reagents to protic agents (water and alcohols) is well known, so that zinc alkoxide formation is a reasonable possibility. The effective directing ability of a methyl ether (*vide infra*) seems to substantiate simple coordination. The yields of the cyclopropanations also support the notion of coordination between the Lewis acidic zinc atom and the oxygen as shown in **ii** (Scheme 3.16). Since 1.2 equivalents of diiodomethane are used, yields of the cyclopropane could not exceed 20% if reaction were occurring through the zinc alkoxide **iii**. However, yields as high as 82% are common in this study. Hydrolysis may be possible, but it is not competitive with methylene transfer, resulting in the formation of the product-zinc iodide complex **iv**. Dauben and Berezin suggest that the *syn* directing effect is a direct result of a transition structure where the zinc reagent is simply coordinated to the hydroxyl group as shown in **ii**. It was proposed that coordination of the zinc reagent to an *axially* disposed hydroxyl is required to account for these observations. This hypothesis was tendered on the reasonable assertion that an axial hydroxyl group is in closer proximity to the double bond than an equatorial group.

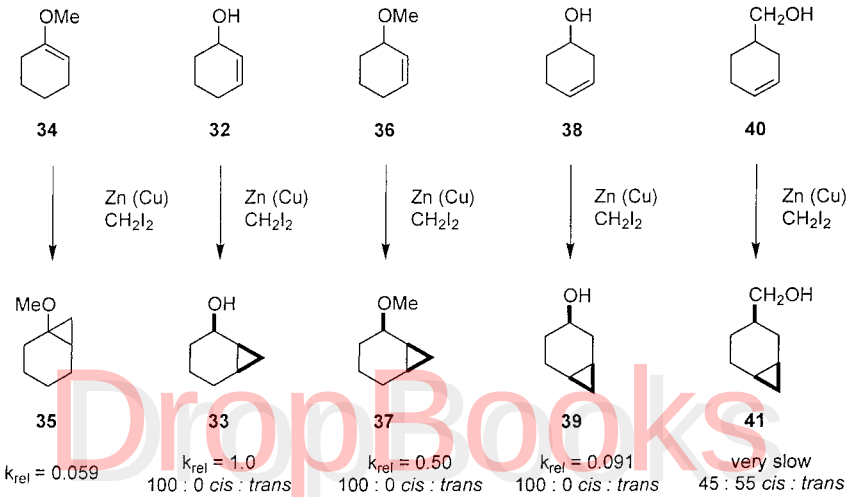


iv **ii** **iii**

Scheme 3.16

In 1968, Chan and Rickborn undertook a more detailed study of this directing effect [13]. Rather than rely on selectivity and yield as indicators of the effect of the oxygen substituent, they examined the *rates* of the cyclopropanations. At this point, little kinetic data was available for this reaction due to technical difficulties involved in monitoring the progress of a heterogeneous process. Simmons and Blanchard had previously determined that cyclopropanation was first order in both alkene and zinc reagent (presuming ICH_2ZnI). Because the concentration of the zinc reagent is difficult to assess, absolute rates could not be determined. Rickborn reasoned that relative rates would be indicative of the influence of the oxygen substituent. In this study a variety of vinylic, allylic and homoallylic alcohols and ethers were surveyed (Scheme 3.17). It is clear that the proximity of the

oxygen substituent has a strong effect on the observed rate enhancement. The greater the distance between the hydroxyl and alkene groups, the slower the reaction. This becomes clear upon comparing alcohols **32**, **38**, and **40**. The reactivity of the enol ether **34** initially appears inconsistent with this trend, but it can be explained by the fact that it is an ether rather than a free hydroxyl group. As can be seen, the methyl ether **36** is less reactive than the corresponding alcohol **32**. In almost all cases, complete *syn* diastereoselectivity is observed. An erosion in stereoselectivity is only observed in the case of the poorly reactive ω-alkenol **40**.



Scheme 3.17

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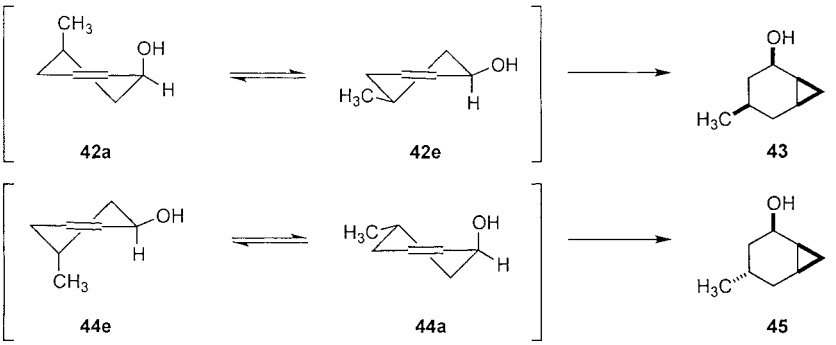
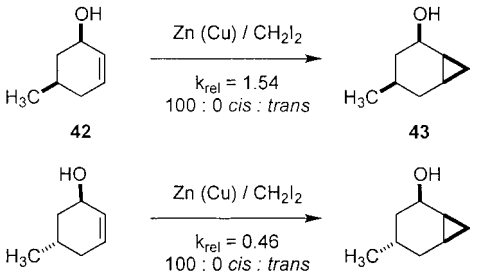
These results illustrate the importance of positioning an oxygen substituent proximal to the double bond for enhanced rate and selectivity. Rickborn also sought to test Dauben and Berezin's earlier conclusions regarding the involvement of an axial hydroxyl group. Unfortunately, the results from alcohols **32** and **38** cannot differentiate the involvement of an axial or equatorial hydroxyl group. Therefore, to test this assertion, Rickborn examined the relative rates of two different substituted allylic alkenols, *cis*- and *trans*-5-methyl-2-cyclohexen-1-ols **42** and **44** (Scheme 3.18). For each of the two isomeric cyclohexenols, two limiting conformations are possible. In the *cis* isomer (**42**), the preferred conformer has both substituents in an equatorial position (**42e**). In the *trans* isomer (**44**) the two conformers are more closely balanced but because of the smaller A value of the hydroxyl group compared to a methyl group (0.54 kcal mol^{-1} compared with 1.74 kcal mol^{-1}), the major conformer should be that with the hydroxyl group axially oriented (**44a**) [38]. If the cyclopropanation occurs through coordination to an axially disposed hydroxyl group as suggested by Dauben, then *trans* isomer **44** should react more quickly. Conformation **44a** of the *trans* isomer is free of *trans*-annular steric interactions which would hinder the reaction through an axial hydroxyl. In the *cis* isomer the conformation that

places the hydroxyl group in an axial position is highly unfavored (**42a**). Moreover, it should be expected that a zinc complex of this compound would not be reactive because of the severe steric interactions between the axial methyl group and the zinc complex. On the other hand, if reaction proceeds through coordination to an equatorial hydroxyl substituent, then the *trans* isomer should react more quickly because of the high population of conformer **42e** compared to **42a**.



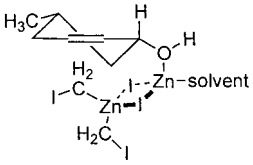
Scheme 3.18

As is apparent from Scheme 3.19, the *cis* isomer **42** reacts three times as quickly as the *trans* isomer **44**. In contrast to the assertion of Dauben and Berezin, the experiments demonstrate that coordination must be occurring through an equatorial hydroxyl group. This result has interesting implications for the mechanism of the methylene transfer. Examination of molecular models shows that it is not possible for an ICH_2Zn unit to bridge the space between the alkene and such a remotely aligned directing group.



Scheme 3.19

To resolve this problem, Rickborn made an ingenious proposal that implicated the intermediacy of a bimetallic transition structure assembly **v** involving a bridging ZnI_2 molecule (Fig. 3.5). This would accommodate the needed spatial requirements of the methylene transfer process. The importance of the polymetallic re-



v

Fig. 3.5 Bimetallic transition state assembly for directed cyclopropanation

agent in the transition state assembly will become clear in the discussion of chirally modified reagents. It should be noted that this conclusion, although well justified, is not universal with respect to all zinc carbenoid-mediated cyclopropanations. There are some cases where Rickborn's conclusion is overlooked in place of the simpler, monomeric zinc model. Rather than there being a single, unified picture for the transition structure assembly, the situation is substrate specific.

The strong directing effect of hydroxyl groups on the diastereoselectivity of the cyclopropanation process is general, although the outcome is not always intuitively obvious. For example, it has often been observed that in large ring cycloalkenols, there are high levels of *anti* diastereoselectivity. This contrasts the high *cis* stereoselectivity observed in 5-, 6- and 7-membered ring systems. Winstein et al. has provided a clear illustration of this selectivity switch and has rationalized it on the basis of the conformational analysis of large ring systems (Fig. 3.6) [39]. In the case of 8-membered rings, where a 99.5 to 0.5 *anti* dr is observed (**46**), one must carefully consider the possible conformations of a cyclooctene. The dihedral angle $\theta(C_1–C_2–C_3–C_4)$ in *cis*-cyclooctene is known to be $\sim 90°$ (Fig. 3.6) [40]. In such a conformation as **vi**, the dihedral angle between the alkene and the hydroxyl becomes $\sim 150°$ $\theta(C_1–C_2–C_3–OH)$). Examination of the full structure shows the disposition of the hydroxyl group relative to the *anti* face of the alkene. Again, careful conformational analysis is able to accurately predict the selectivity of Simmons-Smith cyclopropanations. The mechanistic rationale for the stereoselectivity of the directed cyclopropanation process is maintained. It is interesting to note that similar *anti* diastereoselectivity is also observed in the epoxidation of cyclooctenes with peracids [41].

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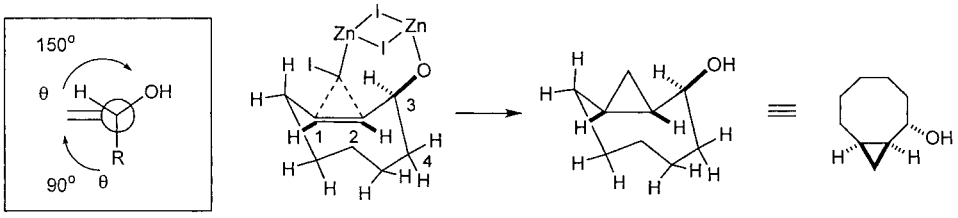


vi 46

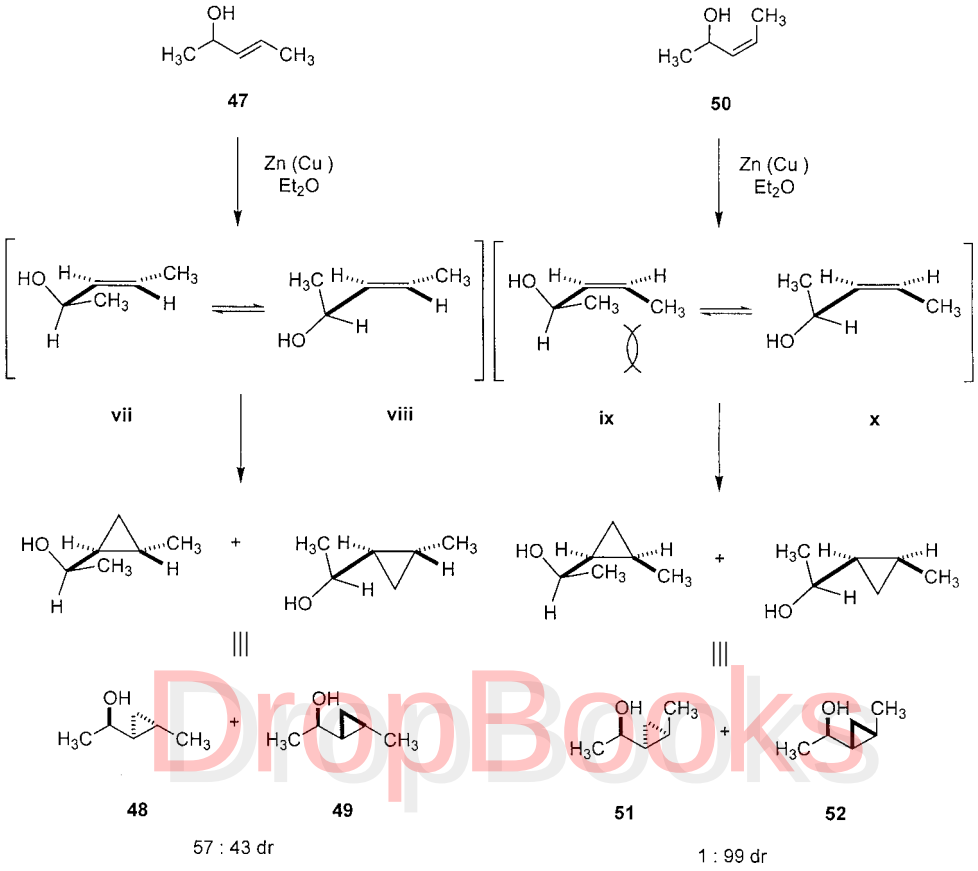
Fig. 3.6 Conformational analysis of the 2-cycloocten-1-ol **46**

High diastereoselectivity is also observed in the cyclopropanation of acyclic allylic alcohols. Despite the conformational flexibility of these systems, they often exhibit high selectivity based on the minimization of allylic strain. Such effects are common to the chemistry of oxygen-directed epoxidations [42], hydroborations [43], dihydroxylations [44], and hydrogenations [45]. So it is not surprising that similar stereoselectivity will be manifest in the Simmons-Smith cyclopropanation, a reaction which is known to be highly dependent on a coordinative interaction. Examination of the reaction of two isomeric 3-penten-2-ols **47** and **50** shows high diastereoselectivity which is strongly dependent on the double bond configuration (Scheme 3.20) [46]. Even though this study was preformed using a racemic mixture of alcohols, information on the relative stereochemistry is still important. The stereochemical imperative of a 150 ° torsional angle between the hydroxyl group and the alkene plane has important consequences for each of the reactive conformations (**vii–x**). In the case of the *E*-substituted alkenol **47**, the inside substituent, either methyl group in **vii** or the H in **viii** avoids serious $A^{(1,3)}$ strain by its disposition $\sim$30 ° above the plane of the alkene. Consequently, poor diastereoselectivity is observed due to the small difference in destabilizing interactions between the two competing transition states. However, the *Z*-substituted alkenol **50** leads to formation of the *syn* diastereomer **52** with high selectivity. The inside group at the allylic position again is lifted 30 ° above the plane of the alkene. In this case though, this twist is not able to alleviate the severe steric interactions between the two methyl groups in **ix**. The difference in $A^{(1,3)}$ strain between *ix* and *x* is much larger than in **47**. The conformer **x** is able to accommodate both the requisite disposition of the hydroxyl group and also avoid serious non-bonded interactions.

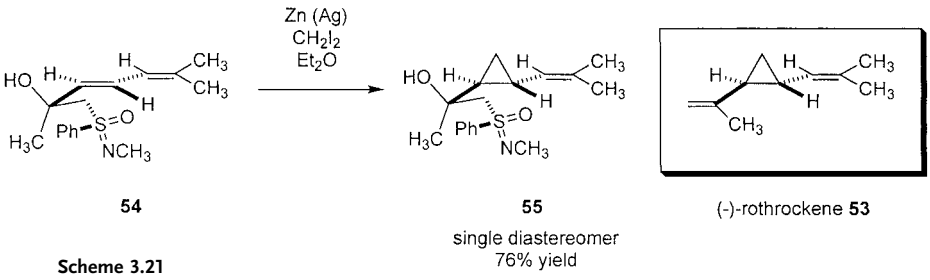
Recently, Charette et al. have also demonstrated this behavior in the stereoselective cyclopropanations of a number of enantiopure acyclic allylic ethers [47]. The high degree of acyclic stereocontrol in the Simmons-Smith cyclopropanation has been extended to synthesis several times, most notably in the synthesis of small biomolecules. Schöllkopf et al. utilized this method in their syntheses of cyclopropane-containing amino acids [48a, b]. The synthesis of a cyclopropane-containing nucleoside was also preformed using acyclic stereocontrol [48c].

Another interesting example of acyclic stereocontrol with an allylic alcohol is seen in the cyclopropanation of *β*-hydroxysulfoximines (Scheme 3.20). The *β*-hydroxysulfoximine functionality is a useful directing group in a number of diastereoselective reactions [49]. In the synthesis of (–)-rothrockene **53**, Johnson et al. attempted the directed Simmons-Smith cyclopropanation of the *E* isomer of the dienyl *β*-hydroxysulfoximine **54** [50a]. As shown in the previous study on acyclic allylic alcohols, such *E* configured substrates typically give poor diastereoselectivities due to the absence of $A^{(1,3)}$ strain. However, in this case, formation of the desired product **55** is exclusive. Clearly, the presence of the neighboring sulfoximine exerts a powerful effect on the process even though coordination of the reagents is most likely occurring through the proximal hydroxyl moiety. A *β*-hydroxysulfoximine has also been used successfully in the synthesis of tricyclic sesquiterpene thujopsene [50b].

Although the previous example involving a *β*-hydroxysulfoximine still relies on the involvement of an alcohol, hydroxyl groups are not unique in their ability to

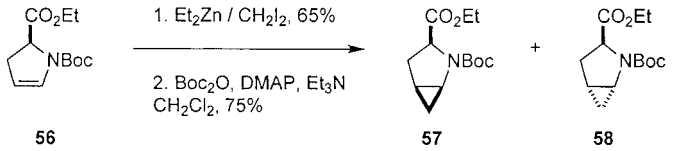


Scheme 3.20



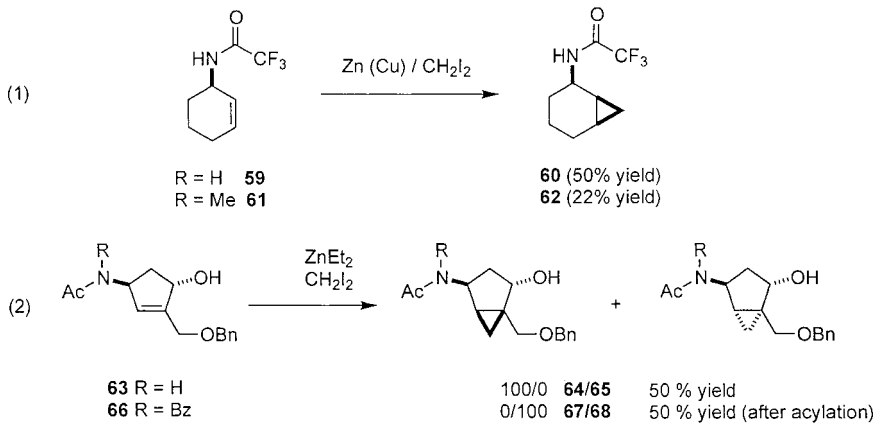
Scheme 3.21

direct the approach of the carbenoid to the alkene. Esters can also serve as directing groups for the cyclopropanation reaction. In the case of the dihydropyrrole **56**, a modest degree of *syn* selectivity is observed (Scheme 3.22) [51]. This sense of diastereoselection is as expected in such a rigid, conformationally biased system.



Scheme 3.22

Coordination of the carbenoid reagent to nitrogen atoms provides a productive interaction as well. Secondary acetamides have been shown to exert a strong directing affect on Simmons-Smith cyclopropanations. A moderate degree of *syn* direction is observed in the cyclopropanation of 1-trifluoroacetamido-2-cyclohexene **59** (Scheme 3.23, Eq. 1) [52]. Formation of the tertiary amide via methylation (**61**) leads to a lessening of the directing effect as evidenced by the decreased isolated yield of the *syn* product **62**. Further studies demonstrate that coordination to an acetamido group may be favored over a hydroxyl group [53]. The cyclopropanation of the disubstituted cyclopentene **63** proceeds with exclusive *syn* diastereoselectivity relative to the acetamide functionality (Scheme 3.23, Eq. 2). Selectivity can be reversed by benzoylation of the acetamide (**66**), re-establishing the directing effect of the alcohol by blocking the coordination site on the amide nitrogen. Despite the compelling nature of this effect, questions regarding the degree of the change in selectivity must be raised due to the low yields observed in the cyclopropanation process.



Scheme 3.23

The discovery of viable substrate-direction represents a major turning point in the development of the Simmons-Smith cyclopropanation. This important phenomenon underlies all of the asymmetric variants developed for the cyclopropanation. However, more information regarding the consequences of this coordinative interaction would be required before the appearance of a catalytic, asymmetric method. The first steps in this direction are found in studies of chiral auxiliary-based methods.

3.4.2 Auxiliary-directed Reactions

3.4.2.1 Chiral Ketals

The powerful influence of an oxygen substituent on the rate and stereoselectivity of cyclopropanation augured well for the development of a chiral auxiliary based approach to asymmetric synthesis [54]. The design of the chiral auxiliary would take into account:

(i) the need to provide a suitable functionality for coordination of the zinc species;
(ii) the means, through a reversible protocol, to attach the auxiliary to the substrate; and
(iii) an effective, asymmetric environment ideally derived from commercially available chiral materials.

Upon removal of the auxiliary, an enantioenriched product could be obtained. The application of chiral auxiliary-based methods to Simmons-Smith cyclopropanation not only provided a useful synthetic strategy, but it also served to substantiate earlier mechanistic hypotheses regarding the directing influence of oxygen-containing functional groups on the zinc reagent [6d].

The use of chiral auxiliaries allows for extension of the Simmons-Smith method to structures which otherwise could not be generated stereoselectively in a single step. In 1990, Mash et al. reported a study of the cyclopropanation of 2-cyclohexenones which were modified by the formation of chiral ketals [55]. In order to access such α-cyclopropyl ketones in a selective manner, a strategy is required to differentiate the enantiotopic faces of the starting enone (Scheme 3.24). The ketal functionality is well suited for this endeavor. Not only does it break the symmetry of the enone moiety through the use of a chiral diol, it provides a site for coordination of the zinc carbenoid. In the absence of the dioxolane oxygens, there is no available site for coordination and thus activation of the carbenoid. Although this strategy may seem more complex than the substrate-directed processes discussed in the foregoing section, it will become clear that similar, stepwise conformational analysis will be able to predict reactivity and selectivity in these important systems.

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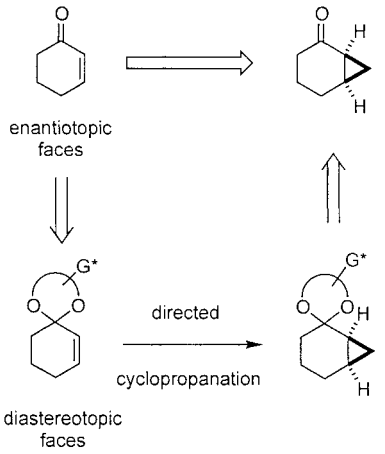
The initial investigation focused on the use of threitol-derived auxiliaries with various substituent groups on the dioxolane ring (Table 3.3). However, it became evident that the oxygen atoms in the substituents had a detrimental effect on selectivity. Comparison of the diastereoselectivities for the ketals **69–71**, which contain Lewis basic sites in the substituents at the 1 and 2 positions, with those from simpler diol derived ketals **72–74** demonstrates the conflicting effects of numerous coordination sites. The simpler, diol-derived ketals provide superior results compared to the threitol derived ketals. The highest diastereoselectivity is observed in the case of the 1,2-diphenylethane-1,2-diol derived ketal **74**.

This unexpected outcome clearly implicated an important stereodirecting role for the dioxolane oxygens. To clarify the significance of having oxygen atoms bound to the stereogenic centers, Mash carried out an important control experiment by exam-

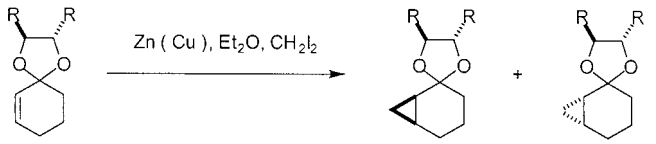


Scheme 3.24

ination of an all-carbon analog of acetal **74**, 2,3-diphenylspiro[4.5]dec-6-ene **75** (Scheme 3.25). The lack of diastereoselectivity in the cyclopropanation of this compound clearly demonstrates the importance of the ketal oxygens.

These remarkable observations stimulated an investigation to understand the origin of the directing effect. To clarify the contribution of the axially- and equatorially-oriented oxygen atoms in the ketal, a survey of the reaction of three conformationally biased *t*-butyl cyclohexenone ketals **78, 81** and **84** was undertaken (Scheme 3.26) [56]. In each case, careful conformational analysis provides critical clues to rationalizing selectivity.

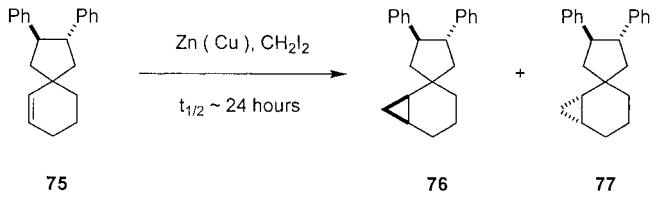
In the conformationally biased cyclohexene ring, the two dioxolane oxygens must assume fixed axial and equatorial positions. Coordination of the zinc carb-



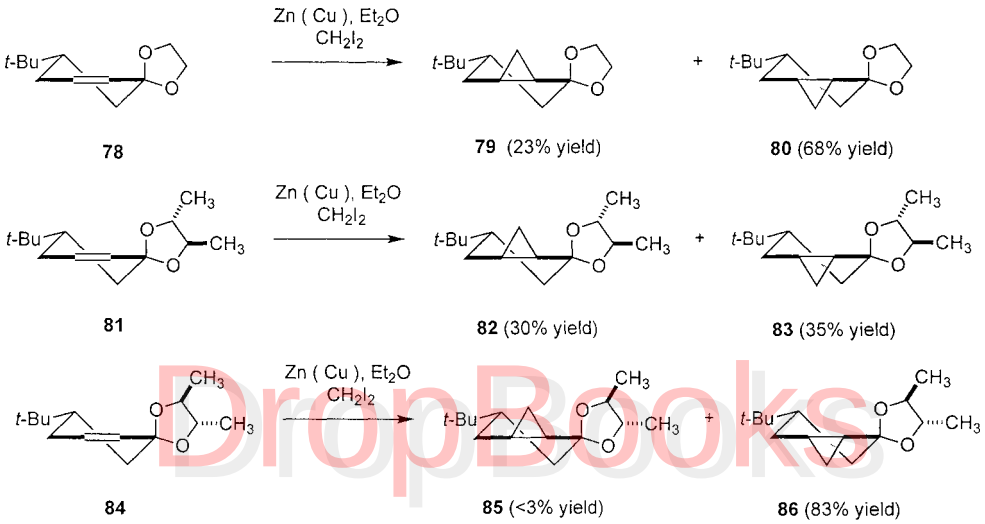
69-74 **A** **B**

Tab. 3.3 Cyclopropanation of cyclohexenone ketals **69–74**

Entry	*Ketal*	*R*	*Yield (%)*	*dr* (A:B)
1	**69**	CH_2OCH_2Ph	86	5:1
2	**70**	CO_2CH_3	37	3:2
3	**71**	CH_2OH	50	1:2
4	**72**	CH_3	86	9:1
5	**73**	$CH_2CH_2CH_2Ph$	92	>9:1
6	**74**	Ph	90	19:1



Scheme 3.25



Scheme 3.26

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enoid to the axial oxygen requires reaction via a transition structure involving a single zinc unit, as proposed by Dauben and Berezin. Coordination of the zinc reagent to the equatorial oxygen requires reaction via a bimetallic zinc unit, much like that proposed by Rickborn. By adopting the conclusions of Rickborn's studies, reaction via the equatorial pathway was assumed. Although this bias is important in all three cases, the reaction of the achiral ketal will give a quantitative value for the selectivity between these two pathways.

Each oxygen atom in the dioxolane has two lone pairs available for coordination to the zinc reagent. In each case, one is proximal to the double bond and one is distal, the latter being too far away to be involved in any kind of productive interaction. The proximal lone pair of the equatorial oxygen substituent is referred to as the "topographically preferred site" (Fig. 3.7).

Further examination of the *chiral* ketals reveals that the lone pairs available for reagent coordination are oriented either in a *syn* or an *anti* relationship to the neighboring methyl substituents. The influence of the chiral auxiliary over the reaction is now clear. If zinc coordination must occur proximal to the double bond,

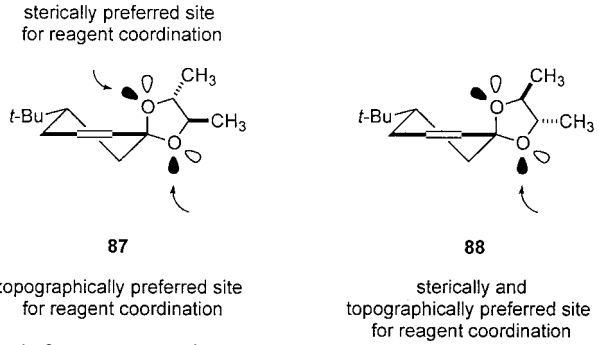

Fig. 3.7 Stereoelectronic rationale for reagent coordination

this coordination will be influenced by the steric demands imposed by the neighboring substituent. The lone pair with the *anti* relationship to the ketal substituent is then the "sterically preferred site". In terms of rationalizing the selectivity for the chiral ketals, topographic and steric effects both contribute to selectivity. In the case of diastereoisomer **81**, conformational analysis shows that these effects are in conflict whereas in isomer **84**, they are cooperative. Selectivity should then be higher in the latter, matched case.

The results for the cyclopropanation of the three ketals confirm these predictions (Scheme 3.26). The unsubstituted ketal **78** shows the inherent selectivity of reaction between the axial and equatorial pathways. Favored reaction via the equatorial pathway is in clear agreement with Rickborn's earlier predictions regarding the reactive conformation. Examination of the two chiral ketals **81** and **84** confirms the prediction of the foregoing conformational analysis. The mismatched case **81** shows a low level of selectivity and reactivity. In the case where the topographic and steric biases are matched (**84**) the selectivity is high. These results stand as an important step in the understanding of the Simmons-Smith cyclopropanation. The ability of conformational analysis to successfully predict the relative reactivity and absolute sense of selectivity for cyclopropanation of these two chiral ketal substrates is in large measure a vindication of the insights provided by earlier mechanistic studies.

3.4.2.2 **Chiral Vinyl Ethers**

Another auxiliary-directed cyclopropanation reaction which provides insights into the nature of the Simmons-Smith process was reported by Tai et al. in 1988 [57]. Chiral vinyl ethers bearing a C_2 symmetric pentanediol auxiliary were found to afford the corresponding cyclopropanes with high diastereoselectivity (Table 3.4). To optimize selectivity, methods for the generation of the carbenoid, as well as solvent and auxiliary structure were investigated. To generate the zinc carbenoid, the authors employed either the original Simmons-Smith procedure (CH_2I_2–Zn–Cu) or a modified Furukawa procedure (5 : 10 equiv. $ZnEt_2/CH_2I_2$). The first substrate to be investigated was the 2,4-pentanediol modified enol ether **89**. By use of the

original Simmons-Smith procedure, a number of ethereal solvents were tested and, in each case, the selectivity is high. A mixture of diethyl ether and dimethoxyethane proves to be best (Table 3.4, entries 1–3). However the high temperatures required for the reaction, the modest yields and the difficulties involved in further diastereomeric enrichment of the product via recrystallization demanded a more selective method be found.

Use of the Furukawa procedure in conjunction with the 2,4-pentanediol-modified enol ether **89** provided more flexibility with regard to the reaction conditions (Table 3.4, entries 4–10). After surveying a number of solvents, diethyl ether, THF and dimethoxyethane were found to be most efficient at affording high selectivities. It is, however, observed that addition of ZnI_2 to the reaction mixture can also raise selectivity (Table 3.4, entries 6 and 8). It is intriguing that this additive is not observed to have an effect on rate or yield. In these reactions, a large excess of the carbenoid reagent is employed (5:10 equiv. $ZnEt_2/CH_2I_2$). Although these conditions still adhere to proportions of the original Furukawa protocol, the use of excess reagent is justified by the gradual decomposition of the zinc carbenoid over the course of the reaction. This is most likely an effect of temperature; typically, the Furukawa conditions employs reduced temperatures.

A simpler solution to obtaining high selectivity is found through use of an enol ether containing a bulkier chiral auxiliary, 2,6-dimethyl-3,5-heptanediol **92** (Table 3.5). Again, a number of conditions were surveyed in order to optimize the reaction. The zinc-copper couple gives high selectivity, but it cannot compare to the exceptional selectivity obtained using the Furukawa reagent. Although selectivity

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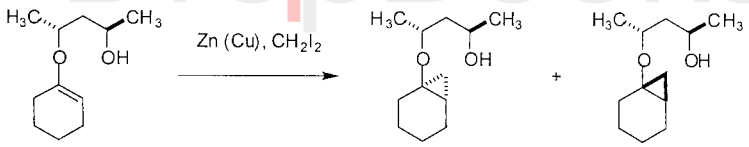
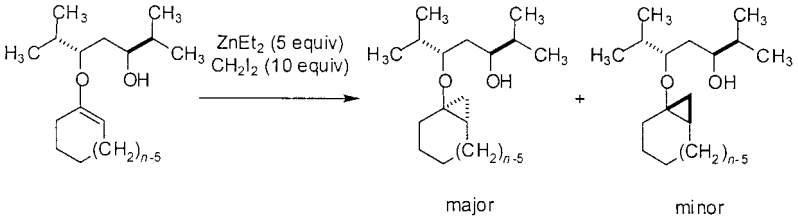


89 90 91

Tab. 3.4 Cyclopropanation of the chiral enol ether **89** under Simmons-Smith conditions

Entry	*Reagent*	*Solvent*	*ZnI_2 (mol%)*	*Temp. (°C)*	*Yield (%)*	*dr (90:91)*
1	Zn(Cu)	THF	0	60	65	90:10
2	Zn(Cu)	Et_2O	0	50	53	94:6
3	Zn(Cu)	Et_2O + DME	0	50	69	95:5
4	$Zn(CH_2I)_2$	Hexane	0	0	52	70:30
5	$Zn(CH_2I)_2$	CH_2Cl_2	0	0	73	86:14
6	$Zn(CH_2I)_2$	CH_2Cl_2	100	0	15	97:3
7	$Zn(CH_2I)_2$	Et_2O	0	0	73	46:54
8	$Zn(CH_2I)_2$	Et_2O	100	0	65	84:16
9	$Zn(CH_2I)_2$	THF	0	20	65	97:3
10	$Zn(CH_2I)_2$	DME	0	20	56	98:2



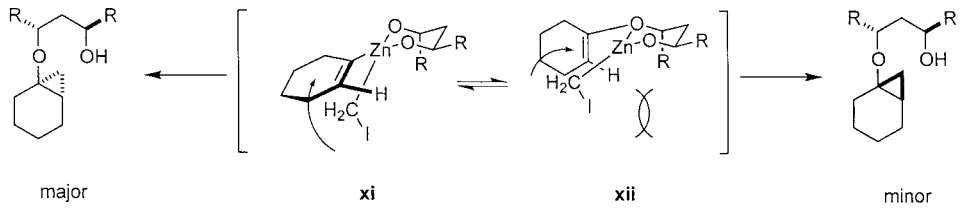
Tab. 3.5 Cyclopropanation of the chiral enol ethers **92–95** under Furukawa conditions

Entry	*Substrate*	*n*	*Yield (%)*	*dr*
1	**92**	5	81	>99:1
2	**93**	6	87	>99:1
3	**94**	7	77	>99:1
4	**95**	8	58	>99:1

is high in a number of solvents, the reaction in diethyl ether at 20 °C is found to be superior in terms of selectivity and yield. Using this auxiliary under the optimized reaction conditions allows for nearly complete stereoselectivity in a number of cyclic enol ether systems (**93–95**). Due to the extraordinary selectivity observed with this auxiliary, further investigations regarding the effect of zinc iodide on rate and selectivity were not preformed.

Once again, careful conformational analysis of the auxiliary provides an explanation for the observed stereochemical outcome (Scheme 3.27) [58]. First, the diol auxiliary can adopt a chair-like, six-membered ring chelate with the zinc carbenoid. Because of the *anti* orientation of the two isopropyl groups in the diol backbone, one is forced to reside in an axial position on the chelate ring. Assuming that the cyclohexene ring takes up an equatorial position, two limiting reactive conformations can then be drawn. In one case, **xi**, the cyclohexene ring is parallel to the plane of the zinc chelate ring. Approach of the methylene unit to the bottom (*re*) face of the alkene yields the observed, major diastereomer. In the other case the cyclohexene ring adopts a perpendicular orientation relative to the chelate ring as shown in **xii**. Here, the carbenoid must approach the top (*si*) face of the alkene. Cyclopropanation via this pathway would then lead to the minor diastereomer. Thus the stereochemical outcome is controlled by the preferred orientation of the cyclohexene ring (*xi*) which in turn can be understood in terms of the unfavorable *syn* pentane type interactions between the forming sp^3 centers and the axial isopropyl group of the auxiliary as in *xii*.

In this model, the intermediacy of a monomeric zinc species is postulated. To support this assumption, an examination of the effect of stoichiometry and solvent in cyclopropanation involving the 2,4-pentanediol auxiliary was preformed [59]. In the initial reaction protocol, a large excess of both diethylzinc and diiodomethane is employed. Such excessive conditions are justified on account of the instability of the zinc carbenoid under the reaction conditions. To minimize the un-



Scheme 3.27

productive process and reveal the most efficient stoichiometry of reagents, the diiodomethane is added to the mixture slowly. This reduces the amount of free carbenoid in solution and thus reduces any decomposition that may be occurring. This empirical survey of reagent stoichiometries demonstrates that a 4:3 ratio of diethylzinc to diiodomethane is required to obtain optimal reactivity and selectivity. The authors propose that under these conditions, in which the zinc carbenoid is still in a large excess as compared to the substrate alkene, are required due to reagent deactivation through strong solvation with the ethereal solvent.

These conditions are quite unusual and deserve further comment. What is particularly interesting is that the diethylzinc is used in molar excess when compared to diiodomethane. The first equivalent of diethylzinc is required to deprotonate the free alcohol, thus forming the ethylzinc alkoxide (ROZnEt) **96** which can then react with diiodomethane to yield the iodomethylzinc alkoxide **97** (Scheme 3.28). Alone, it is unlikely that this species is active in the cyclopropanation. In a careful ^{1}H NMR study, Charette et al. formed an iodomethylzinc alkoxide and observed that in the absence of added organozinc reagent, it was incapable of cyclopropanating the neighboring alkene (Scheme 3.29) [60]. However, the addition of any number of Lewis acidic metal species, including organozinc compounds, could revive the reactivity of the iodomethylzinc alkoxide.

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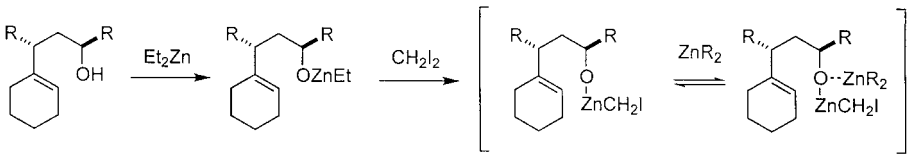
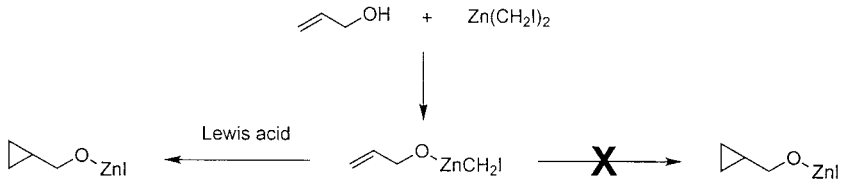


Scheme 3.28 **96** **97** **98**

In light of this fact, one can now propose a role for the excess in the organozinc agents used by Tai. Three organozinc species remain after formation of the iodomethylzinc alkoxide **97** – diethylzinc, $EtZnCH_2I$ and $Zn(CH_2I)_2$. Coordination of any of these Lewis acidic species to the iodomethylzinc alkoxide should allow for the cyclopropanation to proceed through a species such as **98**. This novel bimetallic species forms the putative reactive assembly. The rationale for the added reagents is revealed by later experiments. When a 1:1:1 mixture of diethylzinc, diiodomethane,



Lewis acid = $Zn(CH_2I)_2$, $TiCl_4$, $SiCl_4$, $SnCl_4$, etc ...

Scheme 3.29

and the chiral enol ether is combined, no reaction is observed. Treatment of this solution with another equivalent of diethylzinc then leads to the formation of the product in a 98 : 2 dr and a 42% yield. This result agrees with the mechanistic proposal of a bimetallic, active cyclopropanating species similar to **98**. However, this analysis only accounts for two equivalents of diethylzinc and possibly two equivalents of diiodomethane. Further explanation of the use of reagents beyond this ratio can only be accounted for in light of the aforementioned reagent decomposition.

Although the rationalization of the reactivity and selectivity of this particular substrate is distinct from that for chiral ketals **92–95**, it still agrees with the mechanistic conclusions gained throughout the study of Simmons-Smith cyclopropanations. Still, the possibility of the existence of a bimetallic transition structure similar to **v** (see Fig. 3.5) has not been rigorously ruled out. No real changes in the stereochemical rationale of the reaction are required upon substitution of such a bimetallic transition structure. But as will be seen later, the effect of zinc iodide on catalytic cyclopropanations is a clue to the nature of highly selective reaction pathways. A similar but unexplained effect of zinc iodide on these cyclopropanation may provide further information on the true reactive species.

In addition to providing access to enantiomerically enriched cyclopropane-containing compounds, the auxiliary-direct reactions provide important insights into Simmons-Smith type cyclopropanations [61]. The success of conformational analysis in predicting the reactivity patterns for these substrates is a major advance. One similarity between these disparate methods is that they all rely upon the idea of a bimetallic transition structure. The role of the bridging zinc species (as in **v**) will take on greater significance in subsequent discussions of chirally modified reagents and catalytic methods.

3.4.3
In-situ Chiral Modification

3.4.3.1 Chirally Modified Reagents

An alternative approach to asymmetric synthesis that avoids covalent modification of the substrate is chiral modification of the active reagent. This not only streamlines the number of synthetic manipulations, but it simplifies the isolation of the desired product. In the case of zinc carbenoids, such modifications are feasible alternatives to the use of a standard chiral auxiliary. Two important factors combine

to render this approach viable. First, the success of chirally modified zinc reagents in other reactions should be applicable to cyclopropanation with zinc carbenoids. Most notable among these reactions is the use of complexes of chiral amino alcohols and diethylzinc for the asymmetric alkylation of aldehydes [62]. Second, consideration of Rickborn's proposed transition state assembly **v** in Fig. 3.5 reveals that the ZnI_2 fragment in the bimetallic structure is acting as a spectator. It serves no other role than to bridge the oxygen atom and the active carbenoid. A chirally modified zinc reagent could be reasonably substituted in this position and provide a dissymmetric environment in close proximity to the alkene. On the basis of these factors it seems likely that chiral reagent modification could be successful in the Simmons-Smith cyclopropanation.

In recent years, several accounts of such chiral reagent modifications in cyclopropanation have appeared beginning with an early report by Fujisawa et al. who first demonstrated the concept and its potential (Table 3.6) [63]. Addition of $Zn(CH_2I)_2$ to a preformed zinc alkoxide **100** yields an enantiomerically enriched cyclopropane product **24**. The experimental procedure illustrates how the chirally modified reagent participates in the cyclopropanation. First, the cinnamyl alcohol, diethyl tartrate and diethylzinc are combined in ratio that will provide the bis alkoxide. This bis-heteroatom-substituted zinc species can then interact with the active zinc carbenoid much in the same way as ZnI_2. Now, however, the bridging zinc carries a chiral ligand, introducing a chiral environment in the methylene transfer step. Overall, yield and selectivity are moderate. The selectivity of the process is clearly sensitive to the steric bulk of the ester group. Whereas the ester ligands containing linear alkyl groups such as methyl (**99a**), ethyl (**99b**) and *n*-butyl (**99c**) react with comparable selectivities (approx. 75:25 dr), the bulky isopropyl ester (**99d**) shows a dramatic decrease in selectivity. It is interesting to note that these reactions proceed extremely slowly, requiring almost two days at –12 °C to reach complete conversion. Similarly, slow reactions (*ca.* 24 h) were observed in the BINOL-modified, Simmons-Smith type cyclopropanations explored by Katsuki

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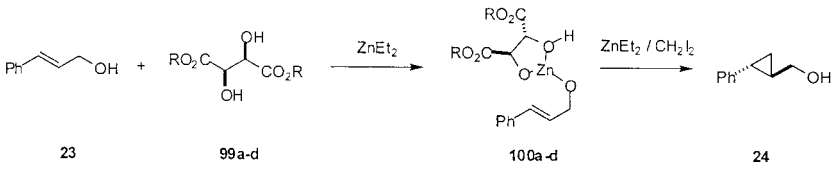
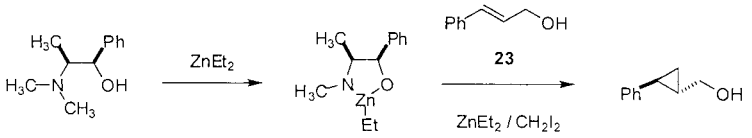


23 99a-d 100a-d 24

Tab. 3.6 Tartrate reagent modification in the Simmons-Smith cyclopropanation

Entry	*Ester*	*R*	*Solvent*	*Temp. (°C)*	*Yield (%)*	*er (24)*
1	**99a**	Me	CH_2Cl_2	0 to RT	12	82:18
2	**99b**	Et	CH_2Cl_2	0 to RT	22	75:25
3	**99b**	Et	$(CH_2Cl)_2$	–12	54	90:10
4	**99c**	*n*-Bu	CH_2Cl_2	0 to RT	17	79:21
5	**99d**	*i*-Pr	CH_2Cl_2	0 to RT	24	64:36



101 102 24

Tab. 3.7 *N*-Methylephedrine reagent modification in Simmons-Smith cyclopropanation

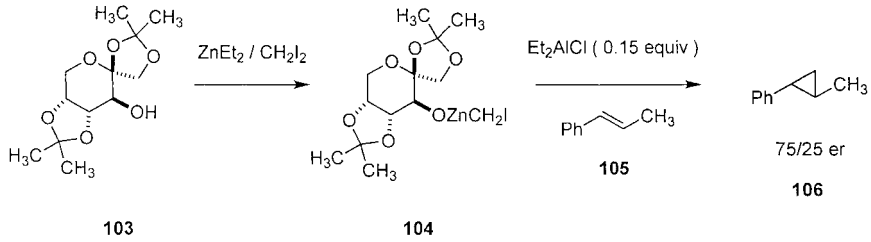
Entry	*Solvent*	*GC Conv. (%)*	*Yield (%)*	*er (24)*
1	hexane	<10	nd	nd
2	toluene	>90	82	59:41 (*R,R*)
3	THF	>90	81	55:45 (*S,S*)
4	DME	>90	85	62:38 (*R,R*)

et al. [34f]. However, these reactions are able to provide high selectivities when compared to Fujisawa's method.

Another method which is in line with the strategy of modifying the spectator zinc species was explored by Denmark et al. (Table 3.7) [64]. The amino alcohol *N*-methylephedrine **101** is a potent ligand for asymmetric aldehyde additions. The zinc-ligand complex **102** is preformed before addition of the alcohol. The $Zn(CH_2I)_2$ is the final reagent added to the mixture and the addition order is similar to that used by Fujisawa. This reagent combination is able to provide the products in moderate yields and selectivities. Although high selectivity is never achieved, even under a variety of conditions, this result is still important because it supports the concept of a bimetallic transition structure with an inactive bridging zinc species.

All chiral reagent modifications do not rely upon an inactive, chiral zinc species. In 1998, Shi et al. undertook an investigation of a structurally unique, chirally modified reagent [23]. Rather than form a chiral zinc species and use it in the place of the bridging ZnI_2, the active cyclopropanating agent is modified directly. By mixing one equivalent of an alcohol with $Zn(CH_2I)_2$, an iodomethylzinc alkoxide is presumed to form. Following the Charette analogy, the iodomethylzinc alkoxide must be activated by a Lewis acid, which in this case is diethylaluminum chloride. In the case of the fructose-derived alcohol **103** a 75:25 er is obtained for **106**, notably with trans β-methylstyrene, a simple alkene (Scheme 3.30).

As part of this study, Shi et al. noted that the reactivity of this oxygen-substituted zinc carbenoid is considerably diminished with respect to the parent zinc species (Fig. 3.8). In the absence of an alcohol ligand (**A**), this protocol leads to a sluggish reaction (approx. 40% conversion after 10 h). This is not surprising in the case of an unfunctionalized alkene [7b]. The addition of some alcohol ligands, such as ethanol (**B**) ($pK_a = 15.9$), 2-chloroethanol (**B**) ($pK_a = 14.3$) and 2,2-dichloroethanol **C** ($pK_a = 12.9$), lead to a suppression of the intrinsic reactivity of the carbenoid [65]. Only weakly basic oxygen containing groups, such as 2,2,2-trifluoroethanol **D** ($pK_a = 12.4$), trifluoroacetate **E** ($pK_a \approx 0.5$) or benzoate **F** ($pK_a = 4.20$), re-



Scheme 3.30

sult in formation of a carbenoid with high reactivity. A possible explanation for this phenomenon is that, once formed, the iodomethylzinc alkoxide has an attenuated Lewis acidity, because of electron donation from the lone pairs of the oxygen. If the electron density at the zinc center increases too drastically, the methylene transfer process is inhibited. This feature explains:

(i) why strong Lewis bases interfere with the reactivity of the zinc carbenoid;
(ii) why **28** is not an active cyclopropanating agent (Fig. 3.3); and
(iii) why such long reaction times are required with Fujisawa's tartrate modified reagent (Table 3.6).

These results are in agreement with Charette's findings regarding the reactivity of in-situ generated iodomethylzinc alkoxides (Scheme 3.29) [60]. The significance of this phenomenon will become important in the design of asymmetric catalysts.

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3.4.3.2 Chirally Modified Substrates

The conceptual complement to the chiral modification of the catalyst is the temporary modification of the substrate. Unlike the chiral auxiliary strategy, temporary substrate modification has greater latitude in introducing the kind of groups

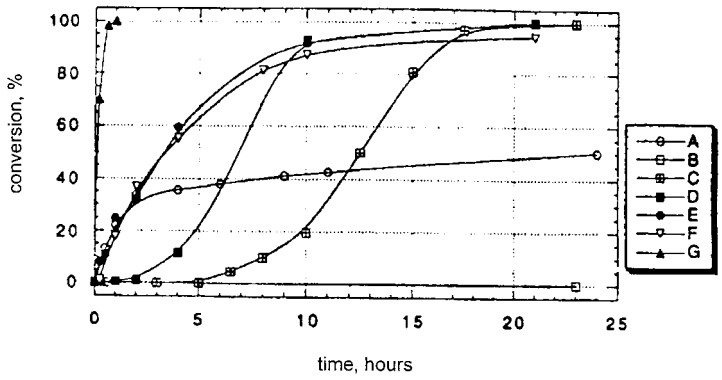
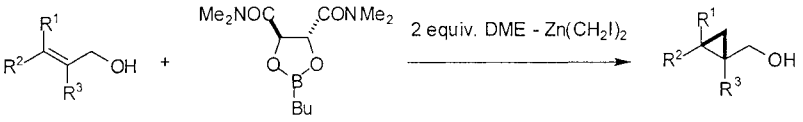


Fig. 3.8 Cyclopropanation of styrene in the presence of alcohol ligands. [Yang, Z.; Lorenz, J.C.; Shi, Y. *Tetranedron Lett.* **1998**, *39*, 8621. Reprinted with permission from Elsevier Ltd.]

that can effectively control the reaction. Because they need not be covalently attached and removed, the modes of binding to the substrate are also more diverse and the directing groups need not be compatible with isolation and purification steps. The success of this approach is best illustrated by the dioxaborolane modifier **108** pioneered by Charette (Table 3.8) [66]. In this design, the dioxaborolane serves a number of roles reminiscent of the ZnI_2 unit in the bimetallic complexes. The trivalent boron atom can coordinate to the hydroxyl group of a substrate alcohol while the zinc carbenoid coordinates to one of the Lewis basic sites in the tartaric acid diamide backbone. Despite the apparent complexity of the dioxaborolane, it is functionally equivalent to zinc iodide. Highly selective cyclopropanation is observed in the presence of a stoichiometric amount of the reagent in a variety of solvents, although dichloromethane proves to be best. The reaction is highly selective for both aryl- and alkyl-substituted allylic alcohols (Table 3.8, entries 1 and 2). Both *E* and *Z* double bond isomers yield highly selective reactions, as do trisubstituted olefins (Table 3.8, entries 3–5). Allylic alcohols containing secondary coordination sites react with high selectivity (Table 3.8, entries 6 and 7). The ethers clearly do not interfere with the selective reaction by providing an alternative site for reagent coordination, a problem that will be addressed again later in the section on asymmetric catalysis. Cyclic allylic alcohols are cyclopropanated with high selectivity as well (Table 3.8, entry 8).

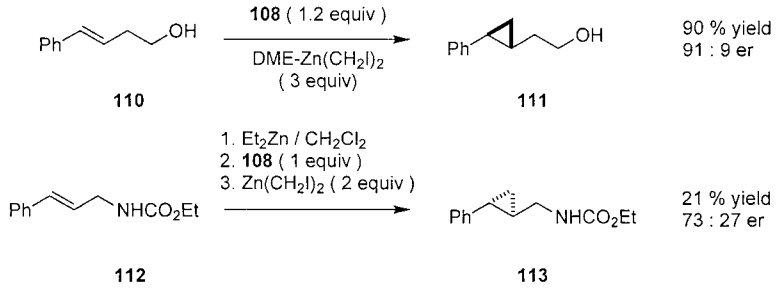
This chiral modifier provides one of the only methods for selective cyclopropanation of substrates which are not simple, allylic alcohols. In contrast to the catalytic methods which will be discussed in the following section, the dioxaborolane has been shown to be effective in the cyclopropanation of a number of allylic ethers [67]. This method has also been extended to systems where the double



107a-g **108** **109a-g**

Tab. 3.8 Cyclopropanation of allylic alcohols with dioxaborolane **108**

Entry	*Alcohol*	R_1	R_2	R_3	*Product*	*Yield (%)*	*er*
1	**23**	H	Ph	H	**24**	>98	97:3
2	**107a**	H	Pr	H	**109a**	80	97:3
3	**107b**	Et	H	H	**109b**	90	97:3
4	**107c**	Me	Me	H	**109c**	86	97:3
5	**107d**	H	Ph	Me	**109d**	96	93:7
6	**107e**	H	$BnOCH_2$	H	**109e**	87	97:3
7	**107f**	$BnOCH_2$	H	H	**109f**	93	96:4
8	**107g**	H	$-(CH_2)_4-$		**109g**	84	80:20



Scheme 3.31

bond is fairly remote with respect to the hydroxyl group (Scheme 3.31). Homoallylic alcohols (**110**) yield cyclopropane products in good yields and with high selectivities. Even allylic carbamates (**112**) can be cyclopropanated with moderate selectivity, albeit in only fair yields.

The stereochemical outcome of this process can be rationalized through analysis of the structure of the dioxaborolane and its interaction with the zinc carbenoid (Fig. 3.9). ^{1}H NMR experiments reveal that CH_3I is produced during the course of the reaction, indicating that the iodomethylzinc alkoxide had been formed. Coordination of the boron activates the carbenoid and allows the methylene transfer to proceed [60]. A crucial stereodirecting component comes from the additional complexation of the zinc atom to the *syn* facial amide oxygen which orients the zinc carbenoid for selective delivery to the alkene. The boron bound butyl group and the allylic alcohol then extend out in staggered, low energy conformations. Such an analysis leads to a correct prediction of the observed configuration of the product.

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The generality of the dioxaborolane method makes it well-suited for synthesis of complex natural products. For example, Nicolaou et al. have successfully used

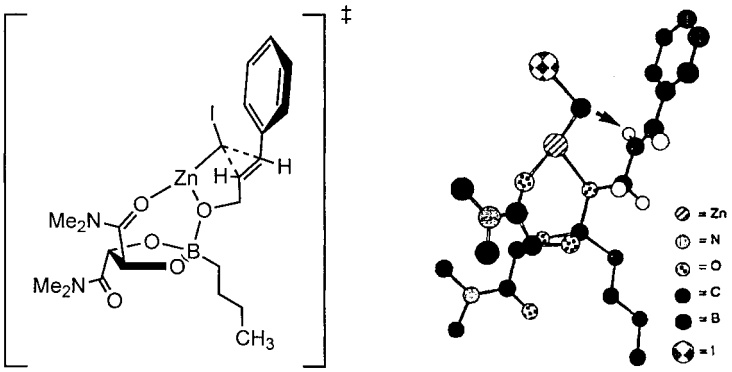

Fig. 3.9 Proposed transition state for cyclopropanation with dioxaborolane **108**. [Charette, A.B.; Juteau, H.; Lebel, H.; Molinaro, C. *J. Am. Chem. Soc.* **1998**, *120*, 11943. Reprinted with permission from The American Chemical Society]

this method to obtain cyclopropane containing fragments required for the synthesis of the biologically active compounds (12*S*,13*S*,15*S*)-cyclopropyl epithilone A [68], plakosides A and B [69].

The exploration of chirally modified reagents was another important step towards a full understanding of the Simmons-Smith cyclopropanation. It also provided two key concepts which will resurface in the discussion of catalytic methods. Considering the work of Fujisawa and Denmark, it can be seen that both their strategies involved formation of a chiral zinc species which was a surrogate for the bridging ZnI_2 proposed in Rickborn's model (**v**, Fig. 3.5). Attachment of chiral ligands at this position surely has an influence over the approach of the carbenoid to the enantiotopic faces of the alkene. The study of the reactivity of iodomethylzinc alkoxides provides a second concept which we be helpful in ligand design for catalytic systems. Highly Lewis basic ligands are a poor choice for any system involving a zinc carbenoid. Both of these factors will become pivotal in the forthcoming discussion.

3.4.4 Asymmetric Catalysis

3.4.4.1 General Considerations

The development of a catalytic system for cyclopropanation based on zinc carbenoids presents a number of challenges that are unique to this reagent and reaction class. Unlike many other organometallic reactions that are amenable to ligand-accelerated catalysis [70], the Simmons-Smith reaction itself proceeds at reasonable rates in the absence of additives. It is thus distinguished from other cyclopropanation processes that employ diazo precursors which can be activated by transition metal complexes bearing chiral ligands. It is also distinguished from the addition of dialkylzinc reagents to carbonyl compounds which does not readily proceed without activation by e.g. amino alcohols [62]. Thus, the major challenge for this transformation is the discovery of a ligand system to catalyze a reaction which does not need ligands! As will be described in this section a solution to this problem was forthcoming in a fashion not unlike what was ultimately found for the dialkylzinc addition process, namely, introducing the activating and stereodirecting functions in a second entity which does not interfere with the reagent.

There are three main criteria for design of this catalytic system. First, the additive must accelerate the cyclopropanation at a rate which is significantly greater than the background. If the additive is to be used in substoichiometric quantities, then the ratio of catalyzed to uncatalyzed rates must be greater than 50 : 1 for practical levels of enantio-induction. Second, the additive must create well defined complexes which provide an effective asymmetric environment to distinguish the enantiotopic faces of the alkene. The ability to easily modulate the steric and electronic nature of the additive is an obvious prerequisite. Third, the additive must not bind the adduct or the product too strongly to interfere with turnover.

The formulation of an additive for zinc carbenoid cyclopropanation that meets these criteria is severely compromised by the by the inherent Lewis acidity of the zinc atom. This Lewis acidity is required for methylene transfer and plays a major

role in the assembly of the putative bimetallic transition state assembly. As has already been noted, strongly Lewis basic ligands such as chiral bis ether **27** inhibit the cyclopropanation process. Although it is possible to substitute halogens with weak Lewis basic groups (e.g. in $ICH_2ZnO_2CCF_3$) [23], it is unwise to expect that another ligand could be directly bonded to the zinc carbenoid and retain reactivity. Further, in asymmetric catalysis, highly Lewis acidic reagents are often plagued by the problem of catalyst turnover [71]. The ligand must then balance the need to associate and control the stereochemical course of the addition, but then dissociate from the product in a rapid and favorable equilibrium.

Although is it possible to delineate the requirements for a suitable catalytic system, reducing this to practice is a daunting prospect. As is the case in many examples of asymmetric catalysis, empirical survey provides the initial leads which, aided by an understanding of the process, allows for accelerated development.

3.4.4.2 **Initial Discoveries**

In 1992 Kobayashi et al. disclosed the first example of a catalytic, asymmetric cyclopropanation by employing a bis-sulfonamide catalyst **114** as an additive (Table 3.9) [72]. The reaction system that was developed for these catalysts involves an allylic alcohol and an unusual stoichiometric combination of diethylzinc and diiodomethane. The C_2-symmetric sulfonamides are fairly weak Lewis bases due to the strong electron withdrawing nature of the sulfonamide group and thus avoid the problems associated with the use of oxygen ligands, which clearly decelerate the methylene transfer step. The reaction proceeds in good yields and selectivities with several aromatic sulfonamides (Table 3.9). In the initial survey, 4-nitrobenzenesulfonamide **114d** proved to be the best ligand, but the parent benzenesulfonamide **114a** was found to be comparable. Curiously, the 3-nitrobenzenesulfonamide ligand **114c** shows much lower selectivity and the results with trifluoromethylbenzenesulfonamides **114e** and **114f** are equally poor. Clearly, the electronic nature of the groups on nitrogen are influential but no trend is apparent.

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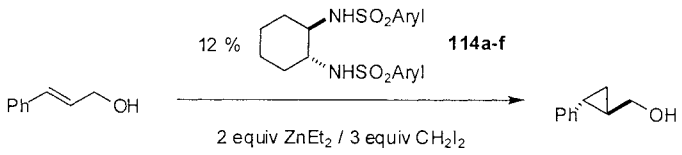
The stoichiometry used for formation of the zinc reagent is noteworthy. Although it is presumed that the Furukawa reagent is being formed in the reaction, the conditions clearly deviate from the original requirement of two equivalents of diiodomethane per equivalent of diethylzinc. A possible reason for this protocol may be rooted in the belief that during deprotonation of the alcohol or the sulfonamide, some the iodomethyl groups may be lost as methyl iodide. Another reason, cited in the study of chiral vinyl ethers, may involve gradual decomposition of the zinc carbenoid. However, this issue is not fully addressed here. The cyclopropanation only proceeds in non-coordinating solvents, such as CH_2Cl_2. Not surprisingly, basic solvents such as Et_2O and THF have an inhibitory effect on the process. The hydroxyl group of cinnamyl alcohol is crucial for enantioselectivity. Whereas allylic methyl ethers react readily, they lead to racemic products. This observation has been interpreted to imply that the ether is capable of coordinative activation of the zinc carbenoid, but that it does not permit association with the chiral ligand-modified species. This hypothesis was tested by examining the cyclopropanation of a number of 2-bu-



23 24

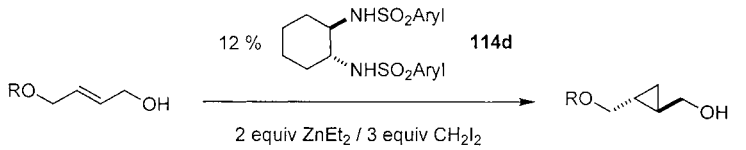
Tab. 3.9 Kobayashi's sulfonamide ligands **114a–f**

Entry	*Catalyst*	*Aryl*	*Yield (%)*	*er (24)*
1	**114a**	C_6H_5	75	66:34
2	**114b**	2-$NO_2C_6H_4$	92	88:12
3	**114c**	3-$NO_2C_6H_4$	72	84:16
4	**114d**	4-$NO_2C_6H_4$	82	88:12
5	**114e**	4-$CF_3C_6H_4$	99	66:34
6	**114f**	3,5-$(CF_3)_2C_6H_3$	99	85:15

tene-1,4-diol derivatives **115** and **117** (Scheme 3.32) [72c]. If coordination with the ether oxygen is competitive with coordination to the alcohol, a product with diminished selectivity should be produced. The cyclopropanation of the mono-benzyl ether **115** proceeds with a significantly lower enantiomeric excess when compared to a simple allylic alcohols. This indicates that reaction through coordination of the reagent to the benzyl ether is competitive. By inhibiting association of the zinc carbenoid through the use of a bulky protecting group (e.g. trityl ether **117**) better selectivity is observed. It is interesting to note that mono-benzyl ethers of this type can be cyclopropanated using Charette's dioxaborolane **108** without a loss in enantioselectivity (Table 3.8).

On the basis of these observations, Kobayashi proposed transition structure **xiii** to account for the enantioselectivity (Fig. 3.10) [72b]. The proposed transition structure properly incorporates elements from previous proposals concerning zinc carbenoid reactivity. By analogy to Rickborn's proposed bimetallic transition structure **v** (Fig. 3.5), this model suggests the involvement of three zinc atoms. The zinc sulfonamide complex assumes the position normally occupied by ZnI_2 in the achiral process. The suggestion that the true catalytic species is the zinc sulfonamide complex rather than the sulfonamide is helpful in rationalizing the activity of the catalyst. In this model, the ligand does not directly activate the reagent. Thus, inhibition of reagent activity and catalyst turnover are not problems since that zinc atom need not dissociate from the ligand. This model suggests the important role of the free hydroxyl group in binding the catalytic species. Without formation of the zinc alkoxide, the assembly loses one important point of attachment, compromising its ability to anchor the chiral zinc-sulfonamide complex.

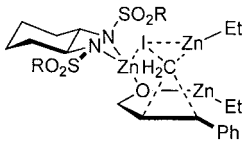
Despite its incorporation of all the reactive components, this model leaves much to be desired. For example, the formation of the zinc alkoxide and zinc sulfonamide



R = Bn **115**
R = Tr **117**

R = Bn **116** 82/12 er
R = Tr **118** 90/10 er

Scheme 3.32



xiii

Fig. 3.10 Transition structure proposal for cyclopropanation with **114**

complexes is advanced without evidence. Further, the nature of the cyclopropanating agent is not clear. Neither does this structure adequately explain the role of the chiral diamine in determining selectivity, nor the origin of accelerated cyclopropanation.

In an effort to improve upon this original system, Imai et al. undertook the investigation of a number of amino acid-derived bis sulfonamide ligands **119** in the cyclopropanation (Table 3.10) [73]. The use of these ligands provides cyclopropanes in exceptional yields while selectivities are comparable to those observed from the cyclohexane-1,2-diamine-based catalysts (**114**). However, an advantage of this ligand system is the opportunity for structural variation at three points, thereby increasing the diversity of available catalysts. Not only can the group attached to the stereogenic center be modified, but each of the sulfonamide groups can be independently varied to optimize selectivity (Table 3.10). Changing the substituent on the ligand backbone as in **119a–c** has little effect on selectivity, unless it becomes too sterically demanding (**119c**). Increasing the size of this group has either a negligible or detrimental effect on selectivity. Changes in the sulfonamide groups as in **119d–f** have a much stronger influence on the selectivity. Whereas a simple steric differentiation between the groups is not beneficial, an electronic differentiation provides the higher selectivity.

Although Kobayashi's transition structure proposal **xiii** could be applied to these systems, the success of these unsymmetrical ligands may be indicative of a high degree of asymmetry being favored in the selective cyclopropanation. The superiority of the ligand **119e**, with individual sulfonamides which are differentiated both sterically and electronically, further supports this notion. A mechanistic rationale for this observation is hard to formulate, but one possible explanation may ascribe a key role to the sulfonyl oxygens. In Kobayashi's transition state two zinc atoms are coordinatively unsaturated. Since zinc prefers to be tetra-coordinate in this oxidation state, intramolecular coordination of one of the sulfonyl oxygens is

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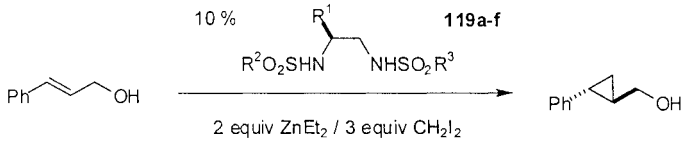


23 24

Tab. 3.10 Cyclopropanation with sulfonamide ligands **119a–f**

Entry	*Catalyst*	R^1	R^2	R^3	*Yield (%)*	*er (24)*
1	**119a**	Me	Ph	Me	100	79:21
2	**119b**	*i*-Pr	Ph	Me	100	79:21
3	**119c**	*t*-Bu	Ph	Me	100	71:29
4	**119d**	Bn	Me	4-$CH_3C_6H_4$	93	91:9
5	**119e**	Bn	Me	4-$NO_2C_6H_4$	100	93:7
6	**119f**	Bn	Me	2,4,6-$(CH_3)_3C_6H_2$	100	88:12

reasonable. By differentiating the two sulfonyl groups as in **119e**, coordination to the relatively electron-rich oxygens of the methanesulfonyl functionality may reinforce the chiral environment provided by the diamine backbone and increase selectivity as shown in **xiv** (Fig. 3.11). The proximity of this electron-rich sulfonyl group to the stereocenter contained in the backbone may be of importance. The involvement of the sulfonyl oxygens in the stereochemistry determining event will later be invoked by Denmark. However, subsequent experiments cast doubt upon the importance of that interaction in their particular system (*vide infra*).

The success of the bis-sulfonamide unit as a ligand in creating an active zinc catalyst suggests its use with other metals in creating active complexes. Changes in the Lewis acidity of the sulfonamide-bound metal may lead to interesting changes in selectivity and reactivity. Titanium-based sulfonamide catalysts do promote the reaction, but the observed enantioselectivity is not comparable with the zinc sulfonamide [72a]. The aluminum sulfonamide complex **120** is also effective in promoting the cyclopropanation of cinnamyl alcohol by the Kobayashi protocol (Scheme 3.33) [74]. Comparable yields and selectivities are obtained by use of the bis-benzenesulfonamide aluminum complex prepared from triisobutylaluminum

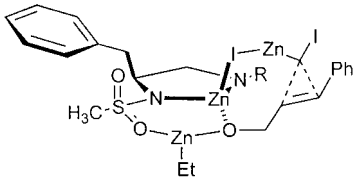
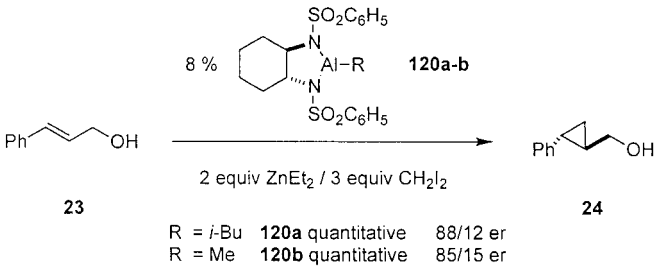


Fig. 3.11 Transition structure proposal for cyclopropanation with electronically differentiated ligands

xiv

(**120a**). Interestingly, the use of trimethylaluminum to prepare the complex (**120b**) leads to slightly lower selectivities. Although it is tempting to interpret these results in terms of the steric bulk of the alkyl substituent in the transition state assembly, no evidence has been forwarded on the nature of the complexes.



Scheme 3.33

The basic motif common to these successful examples is the introduction of a chiral metal complex that can bring together the substrate (perhaps as a zinc alkoxide) and the carbenoid reagent in a chiral environment provided by the ligand. By analogy to the distinction between substrate and reagent modification found with the stoichiometric methods, so too are there two classes of catalytic methods. An approach to temporary substrate modification in asymmetric catalysis was introduced by Charette in 1995. This novel catalytic system is based on the Lewis acidic activation of the allyloxyzinc carbenoid by a chiral titanium species **121** (Scheme 3.34) [60]. Charette had previously shown that iodomethylzinc alkoxides are not capable of intramolecular methylene transfer. After screening a number of additives, it was observed that certain Lewis acids could facilitate cyclopropanation with this previously unreactive iodomethylzinc allyloxide unit. Since chiral Lewis acids are commonly used in asymmetric catalysis, application of a known, successful catalyst may provide some asymmetric induction. The titanium TADDOL complex **121** (well known to promote other asymmetric transformations [75]) is an efficient catalyst for the cyclopropanation of allylic alcohols and provides good levels of selectivity for disubstituted allylic alcohols. Still, the method requires a fairly high catalyst loading. The result with a trisubstituted allylic alcohol shows a considerably lower enantioselectivity. Although a transition state structure that rationalizes the observed selectivity is difficult to formulate, it is reasonable to conclude that the role of the Lewis acid catalyst is probably to activate the zinc carbenoid by withdrawing electron density through complexation of the oxygen, thus introducing a chiral environment around the iodomethylzinc group.

These initial reports demonstrated that a catalytic asymmetric variant of the Simmons-Smith reaction could be developed. Although good yields and selectivities were obtained, the lack of a clear understanding of the origin of activation, the limited structural information on the active species and the absence of a stereochemical model made rational improvements difficult at best. The next

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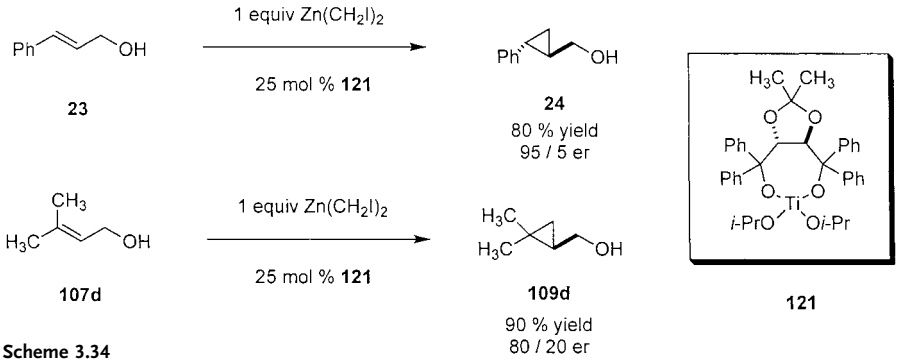

Scheme 3.34

stage in the development of a practical and selective method involved a detailed investigation of the many experimental variables and a in depth study of the nature of the species responsible for the observed selectivity.

3.4.4.3 **Defining the Role of Reaction Protocol**

For a reaction as complex as catalytic enantioselective cyclopropanation with zinc carbenoids, there are many experimental variables that influence the rate, yield and selectivity of the process. From an empirical point of view, it is important to identify the optimal combination of variables that affords the best results. From a mechanistic point of view, a great deal of valuable information can be gleaned from the response of a complex reaction system to changes in, *inter alia*, stoichiometry, addition order, solvent, temperature etc. Each of these features provides some insight into how the reagents and substrates interact with the catalyst or even what is the true nature of the catalytic species.

As part of an independent study of catalytic asymmetric cyclopropanation, Denmark et al. described a systematic investigation of the effect of addition order, stoichiometry and catalyst structure on sulfonamide-catalyzed Simmons-Smith cyclopropanations. Although early studies had shown promising levels of enantioselectivity, higher selectivity would be required for this to be a synthetically useful transformation. The principal issues that were addressed by this study included:

(i) how the substrate allylic alcohol interacts with the catalyst;
(ii) whether the bis-sulfonamide is fully deprotonated and complexed with zinc; and
(iii) determination of the structure of the active catalytic species.

The 1,2-cyclohexanediamine-derived sulfonamide is not unique in its ability to afford enantiomerically enriched cyclopropanes. The efforts at improving the original protocol led not only to higher selectivity, but to a deeper understanding of the nature of the catalytic process.

Denmark et al. explored variations on the original reaction protocol to gain information about the role of the individual reactive components [76]. For these studies,

non-coordinating solvents are employed, either dichloromethane or 1,2-dichloroethane. Because the background reaction is competitive, these reactions are run at –23 °C to suppress the uncatalyzed process. The test substrate is cinnamyl alcohol (**23**) and, in all cases, the Furukawa reagent ($Zn(CH_2I)_2$) is used as the methylene transfer agent. Several pieces of information regarding the cyclopropanation protocol are presented in figures below (Figs. 3.12–3.15 and 3.18). Each figure depicts one of the general protocols examined during the course of the study. The line of reagents in brackets at the top of the figure represents how the reagents are combined and how many flasks are employed. Each set of brackets represents one flask. The equations below this to the left then signify the order in which the reagents are combined or, more often, the order in which the pre-formed reagents are transferred from one flask to the next. Lastly, the graph on the lower right is representative of the rate profile for the *best* sub-protocol in each set. These graphs show that most protocols are conducted both with and without promoter. This measure of the rate enhancement or "split" between the catalyzed and uncatalyzed processes is useful in judging the overall efficacy of the catalyst system in question.

In Kobayashi's original procedure, the sulfonamide catalyst and the alcohol are combined in a single flask before addition of the diethylzinc and the diiodomethane (Fig. 3.12) [72a]. Sub-protocols **Ia** and **Ib** show two of the variations of this original procedure. In both cases, a solution containing the promoter is added to a flask charged with the allylic alcohol. In sub-protocol **Ia** the diethylzinc is added to the alcohol/promoter solution before the diiodomethane. This addition order is found to be superior to the reversed order of sub-protocol **Ib**. Upon examination of the rate profile for sub-protocol **Ia**, the promoter clearly provides a good rate enhancement. The catalyzed process can provide high enantioselectivity (87 : 13 er), although irreproducibility plagues this particular protocol. The beneficial effect of adding the diethylzinc before diiodomethane suggests that deprotonation of the promoter and/or alcohol must precede formation of the zinc carbenoid. It is interesting to note that both the catalyzed and uncatalyzed processes exhibit a long induction period (ca. 60 min). This phenomenon is common to most of the early reaction protocols and will be an important clue to a deeper understanding of the reaction mechanism.

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Whereas this study focused on reaction protocol, the effect of the methylene source on selectivity was another important factor which demanded attention. Earlier studies have demonstrated that substitution of chloroiodomethane for diiodomethane leads to an increased reaction rate (Scheme 3.10) [22]. It is, thus, surprising that the use of chloroiodomethane in sub-protocol **Ia** leads a slower, less selective reaction. In contrast to the use of diiodomethane (~100% conversion at 300 min), the reaction of chloroiodomethane only reaches 58% conversion after 300 min. Selectivity is severely reduced, dropping to 75 : 25 er. The failure of this reagent in the chiral process may be attributed to the obvious differences between the highly polarizable iodine and the more electronegative chlorine atom, although an exact analysis of the difference is not clear.

Having confirmed the importance of independent formation of the zinc carbenoid, other factors could be examined (Fig. 3.13). Protocol **II** was developed to test

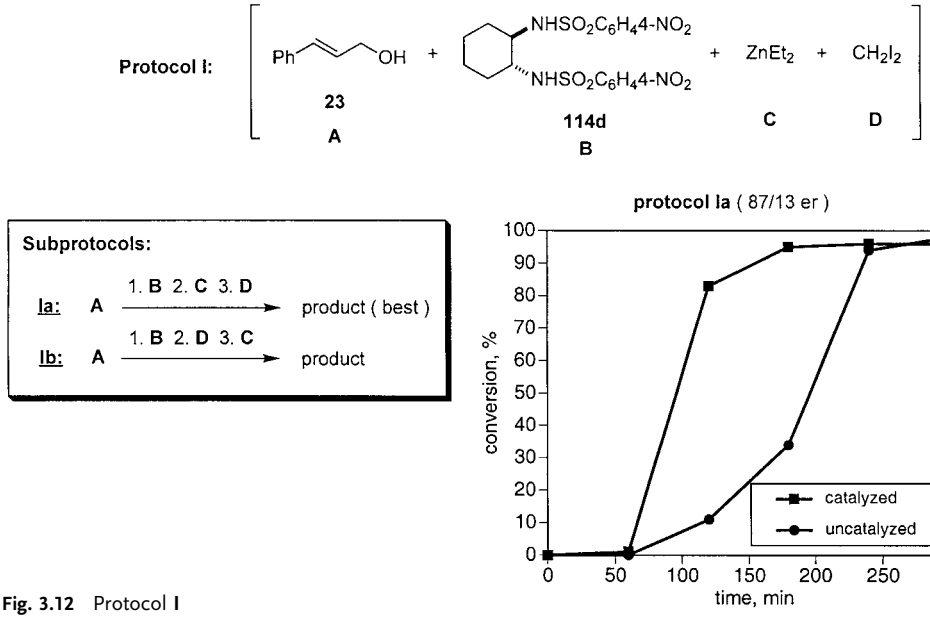
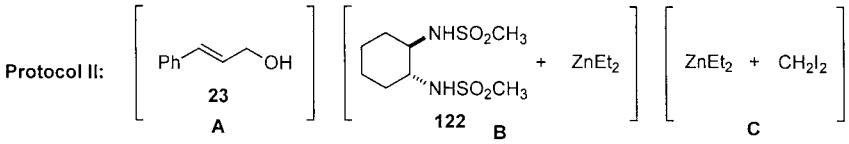
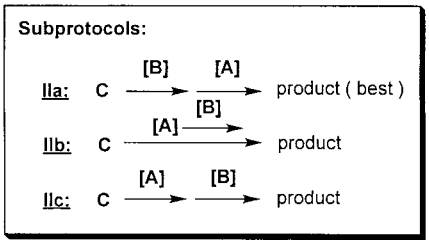


Fig. 3.12 Protocol **I**

for the importance of pre-forming the zinc alkoxide. In these three flask protocols, each reagent could be prepared separately allowing for testing the affect of specific reagent preparations. In all sub-protocols, the alcohol and promoter solutions (**A** and **B**, respectively) are transferred to flask **C**, containing the preformed zinc carbenoid. Flask **B** contains the deprotonated sulfonamide while flask **A** simply contains a solution of the allylic alcohol. In sub-protocol **IIa**, the deprotonated sulfonamide is added to the carbenoid reagent prior to addition of the alcohol. In sub-protocol **IIb**, the sulfonamide solution is mixed with the alcohol prior to addition of this mixture to the flask containing the carbenoid. Sub-protocol **IIc** simply reverses the addition order of **IIa** by adding the alcohol to the carbenoid solution prior to addition of the zinc-sulfonamide. Although each protocol provides a rate enhancement over the uncatalyzed process, none of them is able to provide a rapid and selective reaction. Examination of the rate profile of sub-protocol **IIa**, the best protocol in this sub-set, shows a sluggish reaction which stalls after approximately 3 h. It is surprising that this protocol yields racemic product. The failure of this sub-protocol to yield an enantioselective reaction indicates that the zinc alkoxide is essential for the asymmetric, catalytic reaction. Protonolysis of either the zinc sulfonamide or the zinc carbenoid by this reagent is clearly detrimental.

Having observed that: (i) the zinc carbenoid must be formed prior to addition of the alcohol or sulfonamide; and (ii) that the zinc alkoxide should be preformed in order to obtain high selectivity, the importance of the zinc sulfonamide could be assessed (Fig. 3.14). In this sub-set, flask **A** contains the preformed zinc alkoxide, flask **B** contains the promoter solution and flask **C** contains the preformed zinc carbenoid. In sub-protocol **IIIa**, flasks **A** and **C** are combined prior to addi-





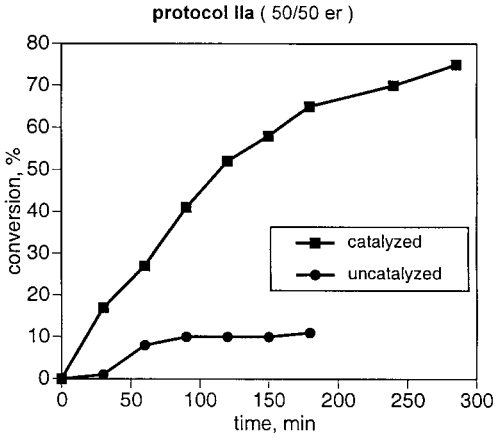


Fig. 3.13 Protocol **II**

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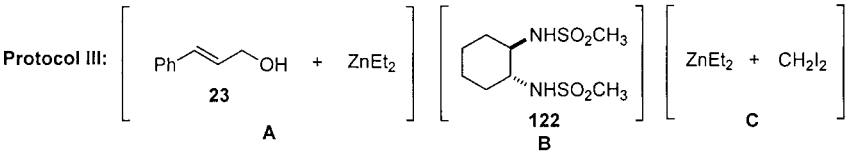
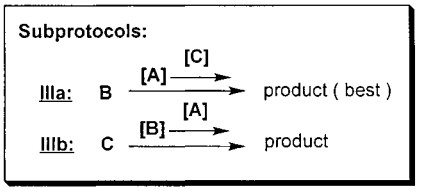
tion to flask **B**. Sub-protocol **IIIb** requires a slightly different addition order, the combine contents of flasks **A** and **B** being transferred to the solution of the zinc carbenoid. Sub-protocol **IIIa** is found to be superior and examination of its rate profile shows an acceptable enhancement over the uncatalyzed process. Again, the unexplained induction period is observed as in the case of sub-protocol **Ia**. Still, the observed 87 : 13 er is comparable with Kobayashi's original procedure. This result suggests that deprotonation of the sulfonamide is *not* a contributor to the selectivity observed in original protocol. Since the sulfonamide is only present in a catalytic amount (10 mol%), its deprotonation by either the zinc alkoxide or the zinc carbenoid may not perturb the system enough to disrupt the selective pathway. However, this result is somewhat misleading.

Although the previous protocol suggests it is not necessary to deprotonate the sulfonamide prior to exposure to the zinc carbenoid, a experimentally simpler procedure can be envisioned wherein the alcohol and promoter are deprotonated in a single flask (Fig. 3.15). In protocol **IV**, the alcohol and promoter are combined in flask **A** and are treated with diethylzinc, thus forming the zinc alkoxide and zinc sulfonamide. In sub-protocol **IVa**, this solution is transferred to flask **C** which contains the zinc carbenoid. Sub-protocol **IVb** represents the reversed addition order. Sub-protocol **IVa** is not only found to be the superior protocol in this sub-set, it is found to out-perform all of the previous protocols! Despite the persistence of the induction period, a large rate enhancement over the uncatalyzed process is observed. This considerable rate enhancement also translates to a reduction in the overall reaction time when compared to sub-protocols **Ia** and **IIIa**. Selectivity rises





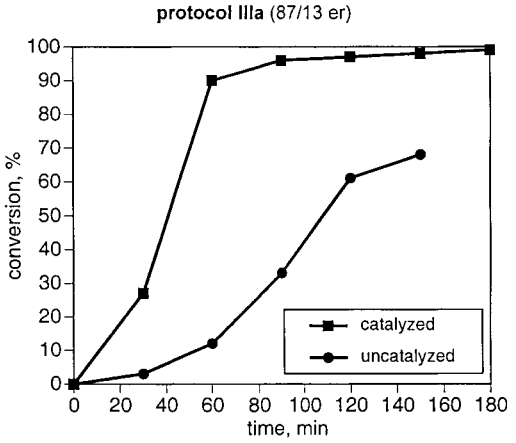
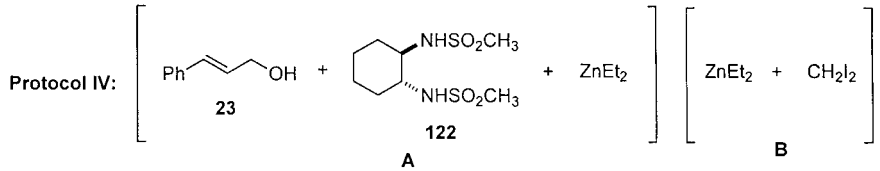
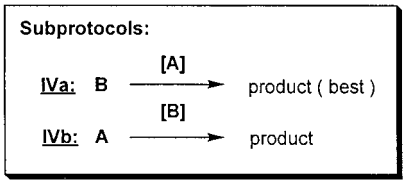


Fig. 3.14 Protocol III





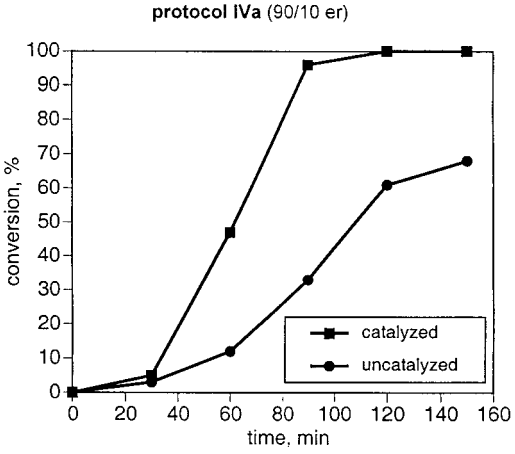


Fig. 3.15 Protocol IV

to 90:10 er using sub-protocol **IVa**. This experiment asserts the importance of preformation of both the zinc carbenoid and the zinc alkoxide. Despite the results of sub-protocol **IIIa**, these experiments have shown that preformation of the zinc sulfonamide complex is key to both the reproducibility of the reaction and to higher selectivities.

Even though these studies provided new insights into the cyclopropanation process, only minor gains in selectivity could be achieved. The question of the induction period still remained [77]. The sigmoidal rate profile is suggestive of an autocatalytic process, i.e., the concentration of the active catalyst increases as the reaction proceeds. This could arise if a by-product of the reaction is necessary for formation of the catalytically active species. Another consequence of such a process would be a difference in enantioselectivity between the early and late stages of the reaction. Fig. 3.16a simultaneously depicts conversion and enantiomeric composition at each time point. Clearly, a strong conversion dependence on the enantioselectivity of the reaction is observed. During the induction period, selectivity is clearly lower, but changes dramatically as the amount of product increases. This indicates that some change in the nature of catalytic species is occurring over the course of the reaction.

Understanding the mechanistic significance of this induction period is aided by contemporary knowledge of the dynamic behavior of zinc carbenoids. The sole by-product of this reaction is ZnI_2. Because zinc carbenoids are subject to the Schlenk equilibrium, one can imagine that the accumulation of ZnI_2 changes the predominant carbenoid species in solution. In the preceding optimization studies, the Furukawa procedure is employed (2:1 CH_2I_2–$ZnEt_2$). On the basis of stoichiometry and previous NMR studies, $Zn(CH_2I)_2$ is the initially formed carbenoid reagent [32, 33], but in accordance with later NMR studies, ICH_2ZnI should form in the presence of ZnI_2 [35]. These studies suggest that iodomethylzinc iodide can become the predominant species, even if $Zn(CH_2I)_2$ is the initially prepared reagent. Hence, the selectivity of the catalyzed process with $Zn(CH_2I)_2$ may differ from that observed with ICH_2ZnI. If the conversion dependence of the enantio-

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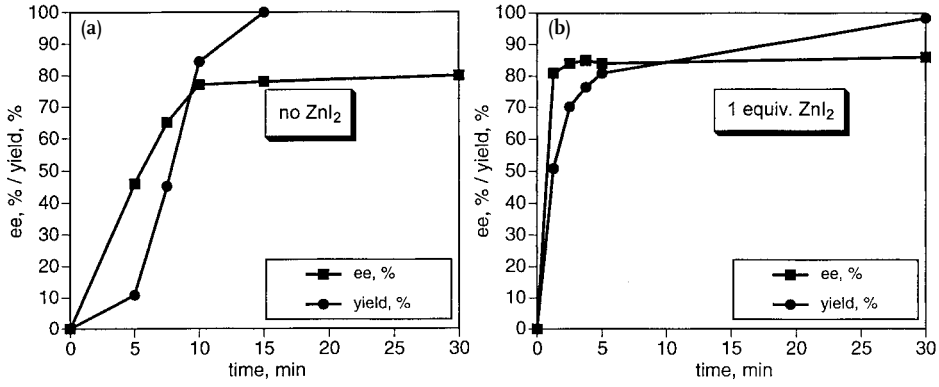


Fig. 3.16 The effect of ZnI_2 on the enantioselectivity of the cyclopropanation

selectivity is recorded for a reaction preformed in the presence of 1 equivalent of ZnI_2, the induction period vanishes and enantioselectivity remains fairly constant (Fig. 3.16b). Presumably, the presence of ZnI_2 at the outset of the reaction rapidly transforms the active zinc carbenoid from $Zn(CH_2I)_2$ to ICH_2ZnI. While the $Zn(CH_2I)_2$ reacts through an unselective pathway, ICH_2ZnI is capable of a competitive reaction through a more selective route.

Proof for the pivotal role of ICH_2ZnI was provided by a combination of product analysis and NMR spectroscopy. Charette had shown that, once formed, ICH_2ZnI does not disproportionate to ZnI_2 and $Zn(CH_2I)_2$ when complexed [35]. This demonstrates that the equilibrium lies to the side of ICH_2ZnI. Thus, as the reaction proceeds and the concentration of zinc iodide increases, the preformed $Zn(CH_2I)_2$ rapidly disproportionates into ICH_2ZnI. Thus, if ICH_2ZnI is preformed and used in the reaction, the induction period should be eliminated. In this study, Denmark devised four routes to produce iodomethylzinc iodide (Fig. 3.17) [77]. The identity of the resulting carbenoid is assessed by formation of the complex with **27** and its analysis by ^{13}C NMR spectroscopy. The four routes are shown below. Although all routes yield a new species which could be assigned as the complex **27**-iodomethylzinc iodide, not all methods gave this material exclusively. Routes 1 and 2 were the cleanest and accordingly also afforded the cyclopropanation product in a good yield and with high enantioselectivities (93:7 er). Routes 3 and 4 produced slower, less selective reactions. The ability to independently generate ICH_2ZnI from a number of routes, confirm its formation by spectroscopy and demonstrate the ability of that species to function under the influence of the catalyst provides compelling support for the intermediacy of iodomethylzinc iodide in the asymmetric process and highlights the importance of the Schlenk equilibrium for creating this species from the initial reagents.

Having established the importance of ZnI_2 in the formation of a protocol which incorporates this pivotal factor was developed (Fig. 3.18) [77]. Flask **A** contains the fully deprotonated alcohol and sulfonamide. Flask **B** contains a solution of ZnI_2 which is generated from the combination of diethylzinc and elemental iodine. This procedure was adopted due to the hygroscopic nature of ZnI_2. By forming the salt in situ under anhydrous conditions, water can be rigorously excluded. Finally, flask **C** contains the preformed Furukawa reagent, $Zn(CH_2I)_2$. The fully deprotonated alcohol and zinc sulfonamide (**A**) are added to a solution of in situ generated ZnI_2 (**B**) prior to transfer of this combine mixture to the zinc carbenoid (**C**). This protocol

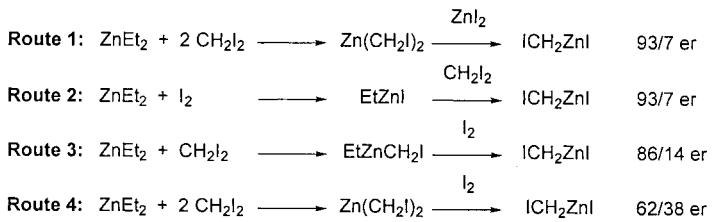
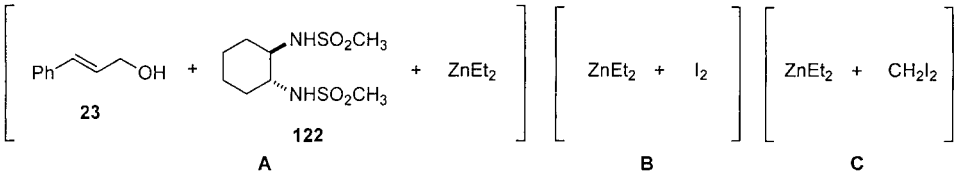
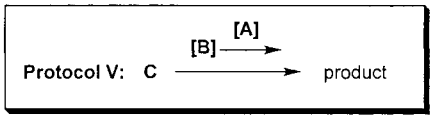

Route 1: ZnEt2 + 2 CH2I2 → Zn(CH2I)2 —ZnI2→ ICH2ZnI 93/7 er
Route 2: ZnEt2 + I2 → EtZnI —CH2I2→ ICH2ZnI 93/7 er
Route 3: ZnEt2 + CH2I2 → EtZnCH2I —I2→ ICH2ZnI 86/14 er
Route 4: ZnEt2 + 2 CH2I2 → Zn(CH2I)2 —I2→ ICH2ZnI 62/38 er

Fig. 3.17 Cyclopropanation under protocol **V** using different zinc carbenoids





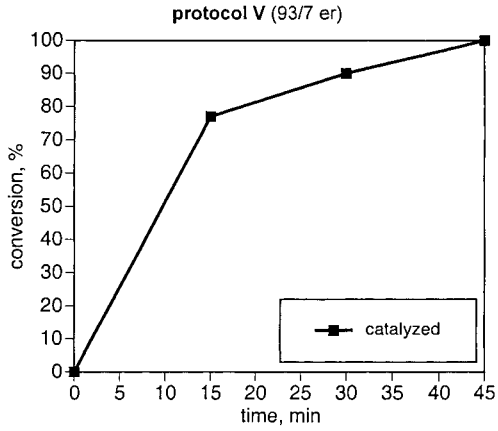


Fig. 3.18 Protocol **V**

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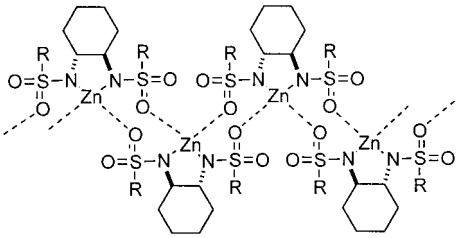
consistently gives a 93:7 er in the cyclopropanation of cinnamyl alcohol; it takes into account all the conclusions of earlier protocol development and clearly benefits from them.

Although this procedure is able to provide the highest selectivities yet observed, a major concern remained the heterogeneous nature of the reaction. Once formed, zinc sulfonamides are only sparingly soluble in dichloromethane [77]. Even dilute solutions of zinc sulfonamides form a gel-like substance which can only be dissolved upon addition of 2,2′-bipyridyl. If the catalytic species is only sparingly soluble in the reaction medium, low catalyst concentrations can contribute to lowered enantioselectivity. This interesting behavior is explained through the proposed formation of a network **76** (Fig. 3.19). Interaction between the Lewis acidic zinc atom of the sulfonamide and the Lewis basic sulfonyl oxygens of neighboring complexes will readily yield a dimer. Further aggregation quickly leads to the formation of the polymer which does not act as a catalyst for the reaction. Hence its formation can be viewed as detrimental to the overall process.

The impact of catalyst polymerization can be seen in the unusual loading dependence of the enantioselectivity (Fig. 3.20a). At low catalyst loadings (<10 mol%), low selectivity can be attributed to competition from the unselective, uncatalyzed pathway. At high catalyst loadings (>20 mol%), selectivity is also dramatically reduced. Higher catalyst concentrations may lead to a greater degree of aggregation. A decrease in the ratio of monomeric to aggregated catalyst would again correspond to increased competition from the unselective, uncatalyzed pathway.

Fig. 3.19 Proposed zinc-sulfonamide network



123

Although reaction is proposed to occur through a monomeric catalyst, the polymeric aggregate **123** may influence the enantioselectivity of the cyclopropanation process. Support for this is derived from the observation of a small, but clearly negative, non-linear effect on product enantioselectivity as the enantiopurity of the catalyst is varied (Fig. 3.20b) [78]. This phenomenon again suggests that there are aggregation processes occurring for the catalyst molecules. Since some non-linear effects are explained in terms of an inactive aggregate, it is attractive to analyze this behavior in terms of the well established "reservoir effect" [79]. In the reservoir effect, an equilibrium between a reactive monomer and an unreactive aggregate is assumed. The stability of the aggregate is affected by how well the molecules interact with themselves (homochiral) or their enantiomers (heterochiral). A negative non-linear effect can be interpreted as a formation of a more stable, homochiral aggregate. Although the current data does not provide for an interpretation of this phenomenon, its existence is clear. The observation of a non-linear effect does agree with the formation of an unreactive catalyst aggregate.

To optimize selectivity, a wide array of diamine backbones were surveyed (Fig. 3.21). However, it appears that 1,2-cyclohexanediamine is unique in its catalytic properties. Only the closely related dihydrophenanthrene ligand **124** could

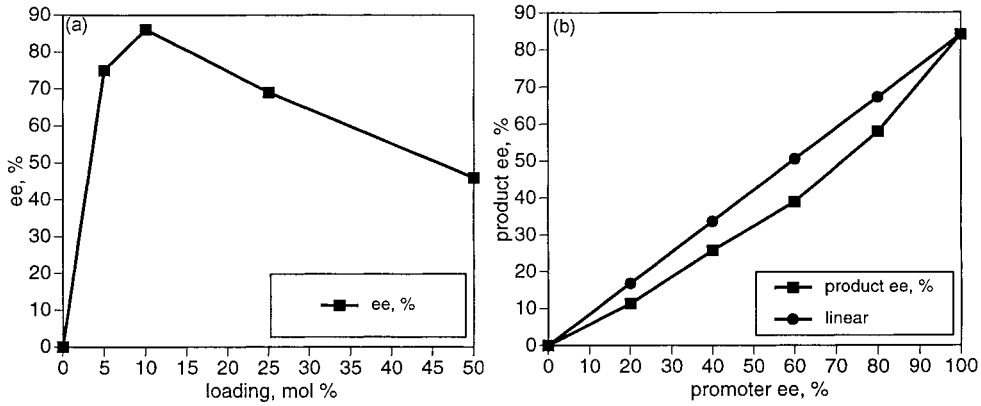


Fig. 3.20 (a) Dependence of enantioselectivity on loading. (b) Non-linear effect on enantioselectivity

match the selectivity observed with the simpler ligand **122**. Upon examination of the other, distinct ligand structures, a number of trends are apparent. First, the dihedral angle is important to catalyst activity and selectivity. Both the 1,2-cyclohexanediamine- and dihydrophenanthrene-derived sulfonamides with angles near 60°, give high selectivities. However, increasing the dihedral angle, as in the 9,10-dihydro-9,10-ethanoanthracene **125** (~120°) or the 1,1′-binaphthyl-2,2′-diamine **126** (~90°), lowers both reactivity and selectivity. Increasing the flexibility of the diamine backbone by use a substituted 1,3-diaminopropane tether as in **128** is a poor choice. Other structural variations, such as use of a sulfonamido ether **129** or a monodentate sulfonamide **130**, also prove unsuccessful.

Another point for structural diversification is the sulfonamide group. Imai had already shown that a wide variety of groups could be introduced at this position to optimize the reaction. Since a wide variety of sulfonyl chlorides are commercially available, a number of different types of groups could be examined (Scheme 3.34). Testing of a variety of aryl and alkyl groups on the 1,2-cyclohexanediamine backbone demonstrates that the simple methanesulfonamide **122** is clearly superior or equal to many other analogs in the cyclopropanation of cinnamyl alcohol (Table 3.11). Another concern which was directly addressed by this survey was the question of catalyst solubility.

The steric bulk of the sulfonamide group has a strong influence over the enantioselectivity of the process. Examination of the Table 3.11 shows that smaller, compact groups allow for higher selectivity. The most selective catalysts contain straight chain alkyl groups such as in **122** and **131a–c**. Branching in the pendant alkyl group as shown in **131d–e** leads to a considerable decrease in selectivity. Aryl groups were able to give high selectivities, as in the case of catalysts **114d**

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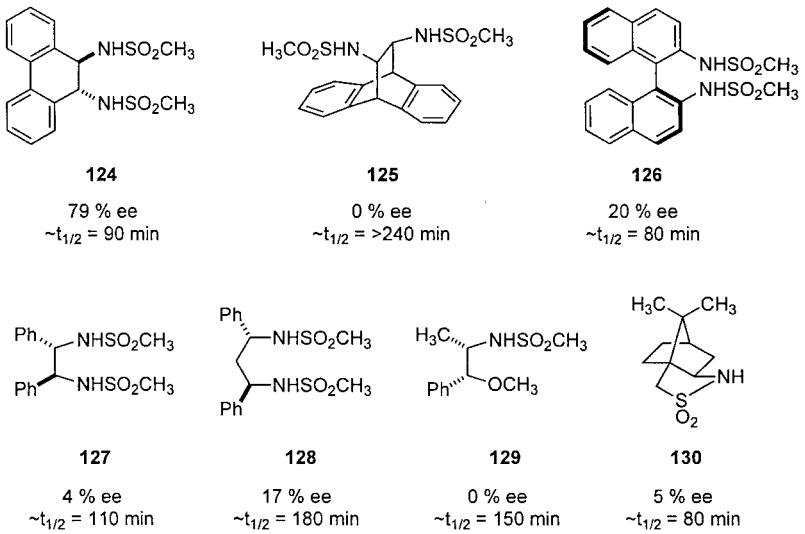
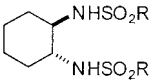


Fig. 3.21 Studies on the diamine backbone



131a-k

Tab. 3.11 Cyclohexane-1,2-bissulfonamides

Entry	*Catalyst*	*R*	*er (24)*
1	**122**	Me	93:7
2	**131a**	Et	90:10
3	**131b**	*n*-Bu	92:8
4	**131c**	*n*-Oct	93:7
5	**131d**	*i*-Pr	86:14
6	**131e**	*t*-Bu	76:24
7	**114d**	4-$NO_2C_6H_4$	89:11
8	**131f**	1-Naphthyl	85:15
9	**131g**	Mesityl	62:38
10	**131h**	CF_3	53:47
11	**131i**	Me/*i*-Pr	92:8
12	**131j**	Me/1-naphthyl	93:7
13	**131k**	CH_3/CF_3	59:41

and **131f**. However, the sterically bulky mesityl group (**131g**) again compromises the selectivity of the reaction.

Because sulfonamides are known to aggregate in solution, it was originally thought that larger, more solubilizing groups could disrupt aggregation and lead to higher enantioselectivities. Many of the catalysts in Table 3.11 show increased solubility relative to the methanesulfonamide **122**. Both the *n*-butyl (**131b**) and *n*-octyl (**131c**) sulfonamides are highly soluble, yet their use does not lead to increased selectivity relative to the methane sulfonamide **122**. The use of bulky alkyl groups such as *t*-butyl **131e** also render the complex highly soluble, but the increased steric bulk around the central zinc atom also compromises selectivity. In the case of these highly solubilizing sulfonamides, it is interesting to note that the final reaction mixture becomes heterogeneous despite the initial solubility of the zinc-sulfonamide complex.

The fluorinated sulfonamide **131h** (entry 10) behaves in a very different manner from the methanesulfonamide **122**. Just as Kobayashi observed, perfluorinated sulfonamides have little in common with their hydrogen-containing analogs. Although CF_3 sterically resemblesan *i*-Pr group, ligand **131h** clearly differs from **131d**, suggesting something beside a steric interaction [80a]. The possibility of zinc-fluorine interactions has been suggested in the literature [80b]. The effect of metal-fluorine interactions has been proposed as an explanation for the unpredictable nature of many fluorinated catalysts [81].

Examination of the results of the unsymmetrical sulfonamides **131i–k** (entries 11–13) reveals an interesting trend. The methyl/*i*-propyl sulfonamide **131i** repre-

sents a major gain in selectivity over the C_2 symmetric isopropylsulfonamide **131d**. A similar gain is observed with the mixed 1-naphthyl (**131j**) and trifluoromethyl (**131k**) sulfonamides. This increase in selectivity may indicate some degree of asymmetry in the stereochemistry determining transition structure. A steric differentiation may be favorable as demonstrated by **131i** and **131j**. However, Imai's earlier results suggest that electronic differentiation may also play a major role. The importance of an electronic effect cannot be ruled out in this system since the unsymmetrical ligand **131k** may give misleading results, because of conflicting metal-fluoride interactions (see **131h**).

Employing protocol **V** with the methanesulfonamide catalyst **122**, a 93:7 er can be obtained in the cyclopropanation of cinnamyl alcohol. This high selectivity translates well into a number of allylic alcohols (Table 3.12) [82]. Di- and tri-substituted alkenes perform well under the conditions of protocol V. However, introduction of substituents on the 2 position leads to a considerable decrease in rate and selectivity (Table 3.12, entry 5). The major failing of this method is its inability to perform selective cyclopropanations of other hydroxyl-containing molecules, most notably homoallylic alcohols.

Understanding the importance of the zinc alkoxide, the iodomethylzinc iodide and the zinc sulfonamide allowed Denmark to propose a revised transition state structure **xv** (Fig. 3.22) [82]. In this picture, the complex, polymetallic aggregate invoked by Rickborn and later by Kobayashi is featured.

In this model, the zinc sulfonamide is bridging the alkoxide and the ICH_2ZnI. On the basis of sulfonamide aggregation and the role that the sulfonyl oxygen plays in that process, a stabilizing interaction between one of the sulfonyl oxygens and the zinc alkoxide is proposed. This interaction can be justified since it yields a stable, tetra-coordinate zinc species. The interaction of the sulfonyl oxygen with the zinc atom of the alkoxide reinforces facial selectivity by orienting the allylic alcohol chain on one side of the carbenoid. The importance of this interaction is supported by the work of Imai, while studies using this catalyst system do not provide unambiguous support (Table 11). Further direction is provided by the

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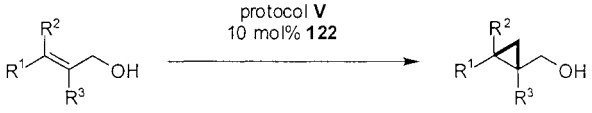
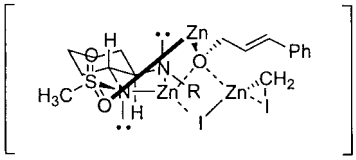


Tab. 3.12 Substrate generality in the cyclopropanation

Entry	*Alcohol*	R^1	R^2	R^3	$t_{1/2}$ *(min)*	*Yield (%)*	*Product*	*er*
1	**23**	Ph	H	H	<3	92	**24**	95:5
2	**132**	$PhCH_2CH_2$	H	H	<3	88	**133**	95:5
3	**134**	Ph	Me	H	<3	92	**135**	95:5
4	**136**	Me	$PhCH_2CH_2$	H	<3	89	**137**	91:9
5	**107e**	Ph	H	Me	7	91	**109e**	51:49

Fig. 3.22 Denmark's transition state assembly

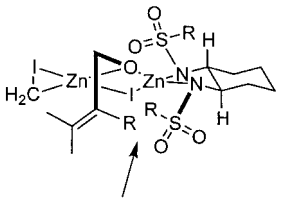


xv

spectator sulfonamide group. An alternative view of the transition state assembly **xvi** makes this clear (Fig. 3.23). To avoid steric interactions with the sulfonamide substituent, the allylic alcohol must extend out from the complex in a zigzag conformation. This interaction may rationalize the failings of bulky sulfonamides such as **131e** and **131g**. The close proximity of this group to the HC(2) of the allylic alcohol also rationalizes the low selectivities observed in the cyclopropanation of 2-substituted allylic alcohols. Close steric contact between the 2-substituent and the sulfonamide R group may destabilize this conformation and open a competing, unselective pathway.

In this model, the zinc sulfonamide acts as an organizational center for the transition state assembly. This agrees with many earlier studies, especially those involving chirally modified reagents, where a chiral zinc species is substituted for ZnI_2. Further support for this hypothesis is provided by an X-ray crystal structure of the zinc sulfonamide catalyst (Fig. 3.24) [83]. This complex of the *n*-butanesulfonamide catalyst **84b** and 2,2′-bipyridyl around a central zinc atom confirms the proposed zinc sulfonamide structure in the hypothetical transition state **xiv**. The highly distorted coordination geometry of the zinc atom greatly enhances its Lewis acidity, rendering it capable of simultaneously coordinating two other components of the cyclopropanation reaction, namely the zinc alkoxide and the zinc carbenoid, ICH_2ZnI.

These optimization studies are an important step in the study of Simmons-Smith cyclopropanations since they allowed for the development of a selective, catalytic method for introduction of a simple methylene unit. However, they also provide insights into the basic mechanism of this process. Together with earlier studies regarding carbenoid structure, the true nature of the reactive carbenoid, ICH_2ZnI, was confirmed. On the basis of these results, a revised transition structure was proposed. Although there is no direct evidence for such a transition



xvi

Fig. 3.23 Alternative view of the transition state assembly

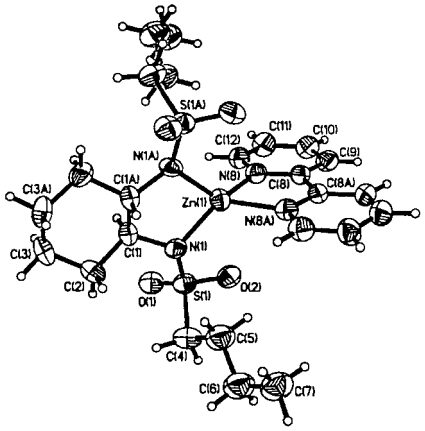


Fig. 3.24 X-ray crystal structure of the **131b**-bipy zinc complex. [Denmark, S.E.; O'Connor, S.O.; Wilson, S.R. *Angew. Chem., Int. Ed. Eng.* **1998**, *37*, 1149. Reprinted with permission from Wiley-VCH]

structure, the X-ray structure does confirm the ability of the zinc sulfonamide catalyst to assume the important role of a chiral, organizational center. This empirically derived model also serves as an important starting point for further investigations into the mechanism of this process.

3.5 Simmons-Smith Cyclopropanations – Theoretical Investigations

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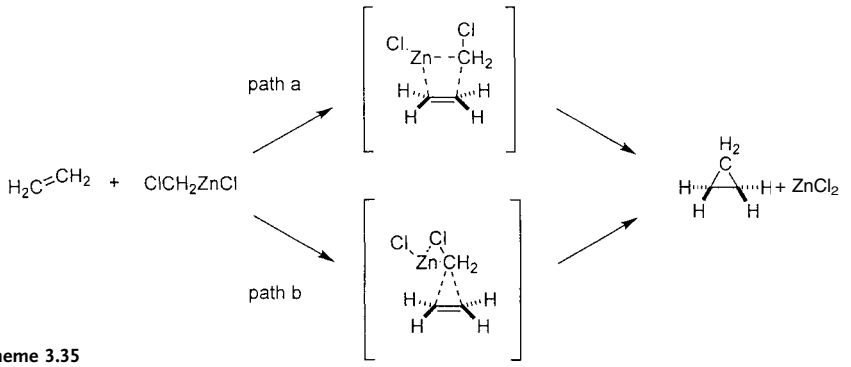
Because of the complexity of the pathway, the sensitivity of the reagents involved, the heterogeneous nature of the reaction, and the limitations of modern experimental techniques and instrumentation, it is not surprising that a compelling picture of the mechanism of the Simmons-Smith reaction has yet to emerge. In recent years, the application of computational techniques to the study of the mechanism has become important. Enabling theoretical advances, namely the implementation of density functional theory, have finally made this complex system amenable to calculation. These studies not only provide support for earlier conclusions regarding the reaction mechanism, but they have also opened new mechanistic possibilities to view.

Early in the study of the Simmons-Smith cyclopropanation, there was a debate regarding the fundamental mechanism of the process. One hypothesis claimed that the methylene transfer is a concerted electrophilic process. A second hypothesis argued for a nucleophilic mechanism akin to a carbometallation reaction. Although the experimental evidence rules out the carbometallation pathway (see Section 3.2) [10], it is still interesting to compare the conclusions from current theory with experimental observations. In 1998, Nakamura et al. computationally evaluated two limiting transition states for the cyclopropanation of ethene by the use of density functional theory (Scheme 3.35) – carbometallation (path a) and direct methylene transfer (path b) [84]. At the B3LYP/6–31G* level of theory, the energetics of the reaction can be evaluated using an intrinsic reaction coordinate

(IRC) analysis. It is found that the methylene transfer (path b) is significantly favored over the carbometallation (path a) by about 13 kcal mol^{-1}. The good agreement between theory and experiment indicates that such studies are valid for this complex system.



Scheme 3.35

The unique behavior of the zinc carbenoid compared with a free carbene has also been rationalized in a computational study. The experimental observation that zinc carbenoids do not undergo the C–H bond insertion processes characteristic of free carbenes has been addressed by Bottini et al. [85]. Again, a comparison between two mechanistic pathways was undertaken. At the B3LYP/6–31G* level of theory, a reaction system involving one ethene molecule and chloromethylzinc chloride can be evaluated (Fig. 3.25). After optimizing the geometries of the reactants and products, an examination of the singlet potential surface for the reaction leads to the identification of four energy minima corresponding to a reactant-carbenoid π-complex, an addition transition state (TS_1), an insertion transition state (TS_2) and a product-zinc chloride complex. Computation of the IRC for the two transition states ($TS_1 + TS_2$) yields data regarding the energetics of the reaction (Fig. 3.25 a). The activation barrier proceeding from reactants to the addition transition state TS_1 is found to be 24.75 kcal mol^{-1}. The activation energy for the insertion transition state TS_2 is much higher, 36.01 kcal mol^{-1}. The energy difference demonstrates that addition is the kinetically favored process, a conclusion which is in complete agreement with experiment. Overall, both reaction pathways are still exothermic, with the insertion channel being almost 10 kcal mol^{-1} more exothermic than the addition channel.

This reactivity pattern can be rationalized in terms of a diabatic model which is based upon the principle of spin re-coupling in valence (VB) bond theory [86]. In this analysis the total wavefunction is represented as a combination of two electronic configurations arising from the reactant (Φ_R) and from the product (Φ_P). The contribution of these two configurations to the overall wavefunction varies as a function of the reaction coordinate. At the outset of the reaction, Φ_R is lower in energy than Φ_P, and hence Φ_R contributes heavily to the overall wavefunction

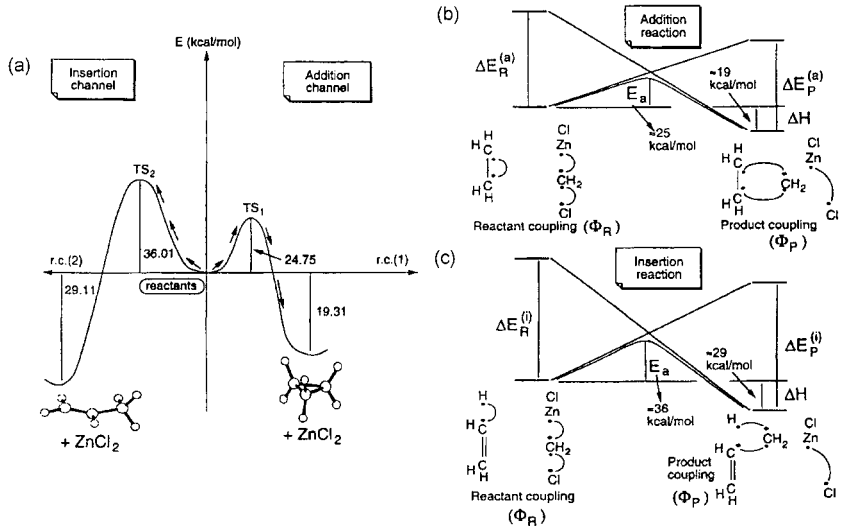


Fig. 3.25 Comparison of insertion and addition reactions of zinc carbenoids. [Bernardi, F.; Bottini, A.; Miscione, G.P. *J. Am. Chem. Soc.* **1997**, *119*, 12300. Reprinted with permission from The American Chemical Society]

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($\Phi_{P(i)} \ll \Phi_{R(i)}$). As the reaction proceeds, the energy of Φ_P decreases relative to Φ_R, they attain degeneracy at the transition state and finally reverse positions upon reaching the products ($\Phi_{P(f)} >> \Phi_{R(f)}$). The position of the transition state and the activation energy (E_a) are then functions of ΔE_R ($\Phi_{P(i)}$–$\Phi_{R(i)}$), ΔE_P ($\Phi_{R(f)}$–$\Phi_{P(f)}$) and ΔH (Fig. 3.25b,c). The analysis shows that ΔE_R for the addition reaction is much smaller than ΔE_R for the insertion reaction. This large difference in ΔE_R can be directly related to the energy difference between a C–C double bond (60 kcal mol^{-1}) and a vinylic C–H bond (108 kcal mol^{-1}) [87]. On the product side, ΔE_P for the insertion reaction is much greater than ΔE_P for the addition reaction. This energy difference can again be rationalized through consideration of the bond energies. The contributions from these different energies, as shown in Fig. 3.25 b and c, lead to a decreased activation energy (E_a) for the addition reaction.

Theoretical analysis has also led to an understanding of the electrophilic nature of the zinc carbenoid. This is well established experimentally – electron-rich alkenes react more rapidly than the electron-deficient compounds [7]. Koch et al. have undertaken a careful investigation at the BLYP/6–31G* level of the frontier molecular orbitals involved in the Simmons-Smith reaction [88]. For this study, two reactive components were considered – ethene and iodomethylzinc iodide. In the addition transition state (TS1), the authors were able to divide the energetic contributions from the ethene and organozinc fragments (Fig. 3.26). Since the energy difference between π_{C-C} and σ^*_{C-I} is much less than the energy difference between π^*_{C-C} and σ_{C-Zn}, it must be concluded that reaction is proceeding via the

former route. Such an orbital interaction is clearly indicative of an electrophilic attack the zinc reagent [89].

In 1998 Nakamura et al. undertook an investigation on the effect of Lewis acids on the Simmons-Smith cyclopropanation [90]. It is well established that Lewis acids such as ZnI_2 play a major role in the cyclopropanation process. The role of the allylic alcohol as a directing group is another important factor which should be considered in any complete theoretical analysis. Most likely due to the complexity of such a calculation, earlier theoretical analyses have neglected these important reactive species when considering the energetics of the system. This ambitious study, conducted at the B3LYP/631A level of theory, examines the behavior and interactions of allyl alcohol, chloromethylzinc chloride and zinc chloride. For the sake of simplicity, the study is broken into three parts.

First, a simple model which incorporates only the zinc chloride and the chloromethylzinc chloride is considered to probe the nature of the Lewis acid activation. Two encounter complexes (RT1 and RT2) and their corresponding transition structures (TS1 and TS2) are found upon examination of the IRC (Fig. 3.27). In RT1, the Lewis acid is activating the carbenoid via binding across the Zn–Cl bond. The approach of ethene to RT1 leads to TS1, in which a 32% elongation of the CH_2–Cl^1 bond occurs. This is interpreted as representing an S_N2-type displacement of chloride by the π-electrons of ethene. Such a nucleophilic attack is consistent with the known electrophilic nature of such zinc carbenoids. In RT2, the Lewis acid is assisting in the departure of the chloride ion bound to the methylene unit. Approach of ethene leads to TS2. Again, a 31% elongation of the CH_2–Cl^1 bond is observed, consistent with a S_N2-type displacement of chloride by ethene. By comparison, RT1 and TS1 are a much more conservative proposals which are in agreement with earlier conclusions regarding the cyclopropanation process. Despite this, theory predicts that the unconventional RT2 is slightly favored by 1.3 kcal mol^{-1}.

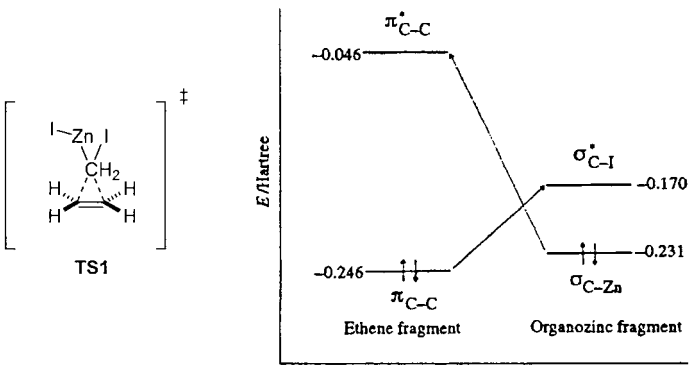

Fig. 3.26 Frontier molecular orbital analysis for the Simmons-Smith cyclopropanation. [Dargel, T.K.; Koch, W. *J. Chem. Soc., Perkin Trans.* **1996**, *2*, 877. Reproduced by permission of The Royal Society of Chemistry]

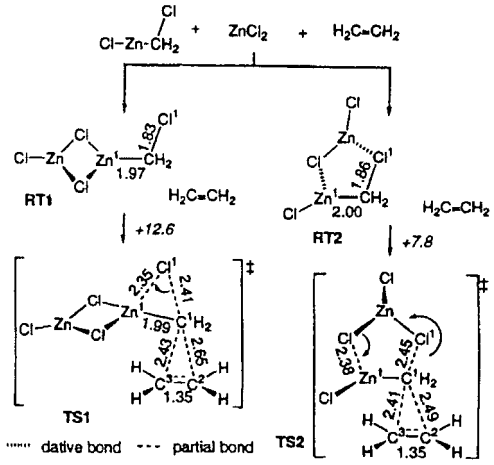

Fig. 3.27 Minimized structures for RT1, RT2, TS1 and TS2. [Nakamura, E.; Hirai, A.; Nakamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5844. Reprinted with permission from The American Chemical Society]

The next step in the calculations involves consideration of the allylic alcohol-carbenoid complexes (Fig. 3.28). The simple alkoxide is represented by RT3. Coordination of this zinc alkoxide with any number of other molecules can be envisioned. The complexation of $ZnCl_2$ to the oxygen of the alkoxide yields RT4. Due to the Lewis acidic nature of the zinc atom, dimerization of the zinc alkoxide cannot be ruled out. Hence, a simplified dimeric structure is represented in RT5. The remaining structures, RT6 and RT7 (Fig. 3.29), represent alternative zinc chloride complexes of RT3 differing from RT4. Analysis of the energetics of the cyclopropanation from each of these encounter complexes should yield information regarding the structure of the methylene transfer transition state.

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Cyclopropanation proceeding through RT3 is calculated to have an activation energy of 35.7 kcal mol^{-1}. Activation of the zinc alkoxide by $ZnCl_2$ as in RT4 (by analogy to RT1), decreases the activation energy for reaction to 29.4 kcal mol^{-1}. Cyclopropanation through the pseudo-dimeric structure RT5 leads to a further decrease in activation energy to 27.9 kcal mol^{-1} when compared to the unactivated RT3. The high energy barrier to cyclopropanation through RT3 is in clear agree-

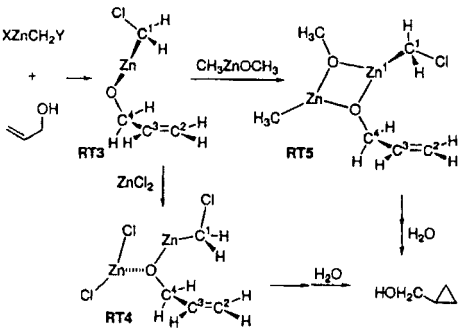

Fig. 3.28 Minimized structures for RT3, RT4 and RT5. [Nakamura, E.; Hirai, A.; Nakamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5844. Reprinted with permission from The American Chemical Society]

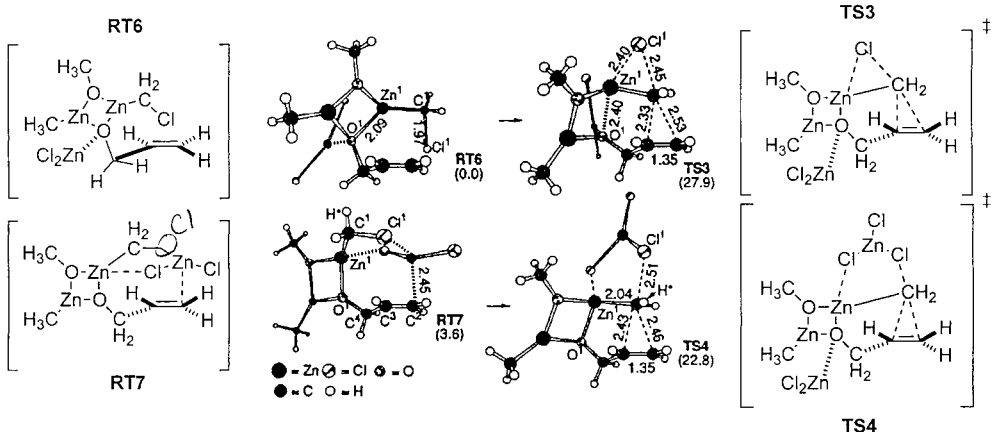

Fig. 3.29 Minimized structures for RT6, RT6, TS3 and TS4. [Nakamura, E.; Hirai, A.; Nakamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5844. Reprinted with permission from The American Chemical Society].

ment with Charette's observation that a simple iodomethylzinc alkoxide is unable to deliver a methylene to the neighboring double bond. However, the slight decrease in the activation barrier for the cyclopropanation seen in RT4 and RT5 still cannot rationalize the high reactivity of the zinc carbenoid.

Examination of cyclopropanation through RT6 and RT7 reveals that a less conventional explanation may be required to rationalize the high reactivity of zinc carbenoids (Fig. 3.29). The structure of RT6 represents a pseudo-dimer as shown in RT5 that has been further activated by coordination of zinc chloride to the oxygen of the chloromethylzinc alkoxide. This mode of activation is reminiscent of that observed in RT1. Cyclopropanation proceeding from RT6 through TS3 has an activation energy of 27.8 kcal mol^{-1}. This represents a negligible decrease in the barrier to methylene transfer when compared to reaction from RT5.

This puzzling result again suggests that the traditional mode of Lewis acid activation (RT1) may not be effective for activation of the zinc carbenoid. Examination of RT7, a structure which represents a pseudo-dimer (RT5) which has been activated by zinc chloride through binding to Cl^1, is an example of Lewis acid activation in the manner of the energetically favored RT2. Cyclopropanation from RT7 through TS4, with its five-membered ring containing the chloromethylzinc group, leads to a lowered activation barrier relative to earlier proposed transition states (22.8 kcal mol^{-1}).

This study suggests a radically new explanation for the nature of Lewis acid activation in the Simmons-Smith cyclopropanation. The five-centered migration of the halide ion from the chloromethylzinc group to zinc chloride as shown in TS2 and TS4 has never been considered in the discussion of a mechanism for this reaction. It remains to be seen if some experimental support can be found for this unconventional hypothesis. The small energy differences between all these competing transition states demand caution in declaring any concrete conclusions.

The activation energy for the favored transition state TS4 (22.8 kcal mol^{-1}) is still somewhat high. Still, the qualitative predictions of enhanced reactivity of the zinc alkoxide-zinc chloride complexes are in full agreement with contemporary ideas about this reaction and represent a major advance in the theoretical understanding of the cyclopropanation process.

3.6 Conclusions and Future Outlook

Since its introduction in the late 1950s, the Simmons-Smith cyclopropanation has ascended as the single most general method for the simple cyclopropanation of alkenes. Although other cyclopropanation methods have proven to be effective, none has yet succeeded in the highly enantioselective transfer of a methylene unit. Aside from its synthetic utility, the Simmons-Smith cyclopropanation has raised many fascinating mechanistic issues that have challenged physical organic chemists throughout its 40 year history. Yet, despite major advances in the understanding of this process, many questions still remain.

This account has attempted to provide an integrated overview of the current understanding of the Simmons-Smith cyclopropanation. Simmons and Smith's original hypotheses about this reaction have provided an excellent foundation for subsequent studies and evolved to form our basis of our current view of the process. Winstein and Dauben's crucial discovery of the powerful directing effect of hydroxyl groups revealed the enabling opportunity for the development of stereocontrol in all of their various incarnations. The landmark insight provided by Rickborn's proposal of a bimetallic transition state assembly represents another major advance that is subsumed by later proposals that rationalize and then design both diastereo- and enantioselective cyclopropanations. The enlightening insights provided by Nakamura's computational analysis may allow further refinement in our understanding of the various components in this deceptively simple process.

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Great strides have been recorded in the invention of stereocontrolled cyclopropanations with zinc carbenoids from auxiliary-directed processes to chiral modifications of the reagent and substrate, to the emergence of catalytic enantioselective variants. Yet, with our current level of understanding and mechanistic knowledge, the generality and selectivity of this reaction are still less than those seen in the most useful of synthetic transformations. Advances beyond these limitations will require substantially new ideas about how to effect selective cyclopropanation. Among the most important challenges are the development of a new class of catalysts that provide a greater enhancement in reaction rate. Although empirical experimentation will always be useful, new advances in theory and in spectroscopic techniques may provide a deeper understanding of the origin of catalysis and suggest opportunities for stereoselection. Further, a current limitation is the requirement for a heteroatom-directing group. A major challenge is the development of a method that will accomplish the enantioselective delivery of methylene to an unfunctionalized alkene on the basis of steric interactions alone.

Whether these advances come from the study of zinc carbenoids, other organometallic sources, diazo precursors or as yet unrecognized sources of methylene transfer, it is our hope that this chapter will serve as a helpful starting point to guide future explorers of this fascinating landscape.

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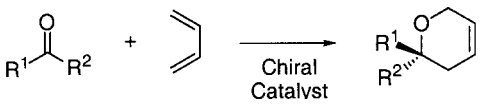
4
Catalytic Enantioselective Cycloaddition Reactions of Carbonyl Compounds

Karl Anker Jørgensen

4.1
Introduction

The cycloaddition reaction of carbonyl compounds with conjugated dienes, known as the hetero-Diels-Alder reaction, has, since its discovery, been one of the cornerstone reactions in organic chemistry for the construction of, e.g., six-membered rings containing an oxygen atom [1]. In the last two decades the development of cycloaddition reactions of carbonyl compounds with conjugated dienes has mainly focused on reactions leading to optically active compounds. The reason for the interest in obtaining optically active compounds by use of cycloaddition methodology is that the reactions are normally easy to perform and generally highly regio- and diastereoselective. Furthermore, the cycloaddition reaction of a carbonyl compound with a diene can give up to four new chiral centers. The enantioselective version, especially when promoted by chiral Lewis acid complexes, has further enhanced its power in the synthesis of optically active compounds [2].

This chapter will focus on the development of catalytic enantioselective cycloaddition reactions of carbonyl compounds with conjugated dienes (Scheme 4.1) [3].



Scheme 4.1

4.2
Activation of Carbonyl Compounds by Chiral Lewis Acids

The main strategy for catalytic enantioselective cycloaddition reactions of carbonyl compounds is the use of a chiral Lewis acid catalyst. This approach is probably the most efficient and economic way to effect an enantioselective reaction, because it allows the direct formation of chiral compounds from achiral substrates under mild conditions and requires a sub-stoichiometric amount of chiral material.

To achieve catalytic enantioselective cycloaddition reactions of carbonyl compounds, coordination of a chiral Lewis acid to the carbonyl functionality is necessary. This coordination activates the substrate and provides the chiral environment that forces the approach of a diene to the substrate from the less sterically hindered face, introducing enantioselectivity into the reaction.

When choosing a chiral Lewis acid catalyst for a reaction, many factors must be taken into account. The carbonyl compound should be able to coordinate to the Lewis acid and have sufficient reactivity. The choice of Lewis acid in combination with a chiral ligand is of particular importance. The Lewis acidity, the structural properties of the metal complex, and the electronic and structural properties of the chiral ligand, should all be considered. The main group metals such as aluminum, boron, the hard early transition metals titanium and zirconium, and some lanthanide elements are all oxophilic metals which have been widely used in combination with chiral ligands containing oxygen as the coordinating atoms for the cycloaddition reaction of carbonyl compounds. Chiral ligands containing nitrogen atoms for coordinating have broad flexibility toward both hard and soft metals and great success has been achieved by applying these ligands in combination with soft metals. Ligands containing phosphorus as the coordinating atoms are soft ligands and success has also been achieved applying these ligands in combination with soft metals, for example palladium and platinum.

The catalytic enantioselective cycloaddition reaction of carbonyl compounds with conjugated dienes has been in intensive development in recent years with the main focus on synthetic aspects; the number of mechanistic studies has been limited. This chapter will focus on the development and understanding of cycloaddition reactions of carbonyl compounds with chiral Lewis acid catalysts for the preparation of optically active six-membered ring systems.

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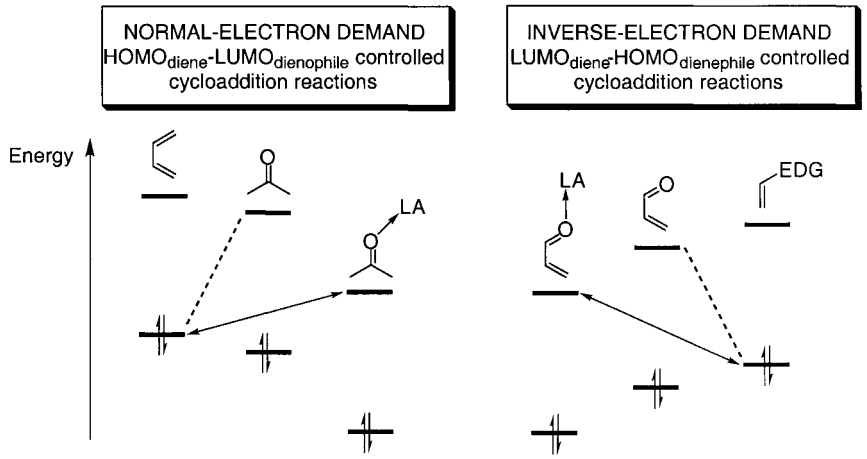
4.2.1 The Basic Mechanisms of Cycloaddition Reactions of Carbonyl Compounds with Conjugated Dienes

The cycloaddition reactions of carbonyl compounds with conjugated dienes cannot be discussed in this context without trying to understand the reaction mechanistically. This chapter will give the basic background to the reactions whereas Chapter 8 dealing with theoretical aspects of metal-catalyzed cycloaddition reactions will give a more detailed description of this class of reactions, and others discussed in this book.

Most reactions discussed can be classified into two types of $[_{\pi}2_s + _{\pi}4_s]$ cycloadditions, the normal and inverse electron-demand cycloaddition reactions, based on the relative energies of the frontier molecular orbitals of the diene and the dienophile (Scheme 4.2) [4].

The normal electron-demand reaction is a $HOMO_{diene}$-$LUMO_{dienophile}$-controlled cycloaddition which predominantly occurs between electron-rich dienes and electron-deficient dienophiles (Scheme 4.2, left dotted line). The inverse electron-demand cycloaddition reaction is primarily controlled by a $LUMO_{diene}$-$HOMO_{dienophile}$ inter-



Scheme 4.2

action which can be found for, e.g., enones and hetero analogs reacting with alkenes with electron-donating groups (Scheme 4.2, right dotted line).

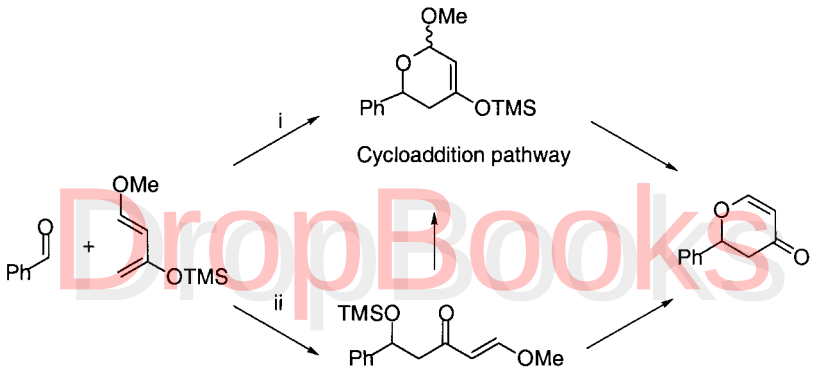
The basic concept of activation of the carbonyl compound is to utilize the lone-pair electrons of the oxygen atom for coordination to the Lewis acid. The coordination to the Lewis acid changes the frontier molecular orbitals of the dienophile and, for the normal electron-demand reactions, a decrease of the LUMO and HOMO energies is observed leading to a better interaction with the dienophile (Scheme 4.2, left full line). The energy difference between the $HOMO_{diene}$ and the $LUMO_{dienophile}$ is thus reduced compared with the absence of a Lewis acid; this accounts for the activating effect of the Lewis acid. The catalytic properties of the Lewis acid for the inverse electron-demand cycloaddition reaction are due to the coordination of the Lewis acid to the oxygen atom of the 1,3-diene; this leads to a decrease of the $LUMO_{diene}$ and $HOMO_{dienophile}$ energies and, thus, based on a frontier molecular orbital way of reasoning, more favorable interaction with the electron-rich alkene (Scheme 4.2, right full line). Furthermore, the coordination to the Lewis acid also alters, to some extent, the distribution of the atomic orbital coefficients of the dienophile and the 1,3-diene. The LUMO atomic orbital coefficient at the carbonyl carbon atom increases, which makes it more susceptible to nucleophilic-like attack by the diene. This polarization can, however, also influence the reaction mechanism. It has been pointed out that the cycloaddition reaction can change from a concerted non-synchronous mechanism to a stepwise mechanism, depending on the substituents on the reacting species and the reaction conditions.

The stereochemistry of the product formed in the cycloaddition reaction depends on the approach of the substrate. There are two different approaches by which the reaction can proceed – *endo* and *exo*. For the reaction of, e.g., a β,γ-unsaturated α-keto ester with an ethyl vinyl ether there are four possible approaches

leading to four diastereomers, as the β,γ-unsaturated α-keto ester can have both *E* and *Z* geometry. The diastereoselectivity of the cycloaddition reaction of carbonyl compounds is affected by the presence of Lewis acids. The uncatalyzed reaction of aldehydes is usually *endo*-selective for the carbonyl substituent [5]. In the presence of Lewis acids as catalysts it has been proposed that the Lewis acid is oriented *trans* to the carbonyl substituent and that modest *endo* selectivity usually observed is because of a preference for the solvated Lewis acid being *exo*, because of its size [6].

For the reaction of carbonyl compounds with conjugated dienes two mechanistic pathways have generally been taken into account when Lewis acid-catalyzed reactions are considered:

(i) a traditional cycloaddition; or
(ii) formation of the cycloaddition product via a Mukaiyama aldol pathway as outlined in Scheme 4.3.



Scheme 4.3 Mukaiyama-aldol pathway

There have been few mechanistic studies of Lewis acid-catalyzed cycloaddition reactions with carbonyl compounds. Danishefsky et al., for example, concluded that the reaction of benzaldehyde **1** with *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-dimethyl-1,3-butadiene (Danishefsky's diene) **2** in the presence of BF_3 as the catalyst proceeds via a stepwise mechanism, whereas a concerted reaction occurs when $ZnCl_2$ or lanthanides are used as catalysts (Scheme 4.3) [7]. The evidence of a change in the diastereochemistry of the reaction is that *trans*-**3** is the major cycloaddition product in the BF_3-catalyzed reaction, whereas *cis*-**3** is the major product in, for example, the $ZnCl_2$-catalyzed reaction – the latter resulting from *exo* addition (Scheme 4.3).

The reaction course of the cycloaddition reaction can also be dependent on the Lewis acid complex used as the catalyst. When the substrate contains an allylic C–H bond, both a cycloaddition and an ene reaction can occur. In the reaction of glyoxylate **4** with 2,3-dimethyl-1,3-butadiene **5** both the cycloaddition product **6**

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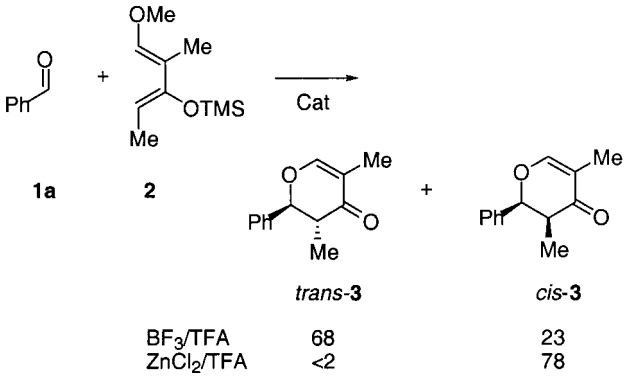
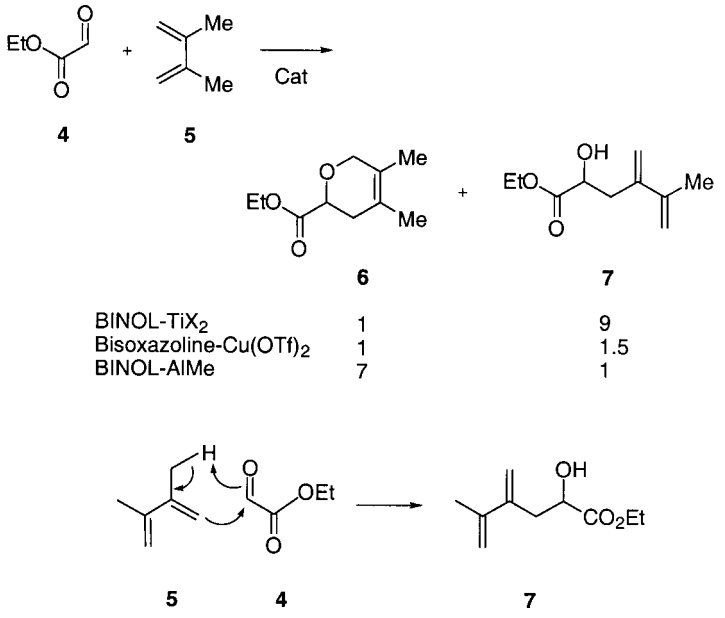


Scheme 4.4

and ene product **7** can be obtained (Scheme 4.5). By using BINOL-titanium(IV) complexes as the catalyst, the ene product **7** is the major product, with a **6**:**7** ratio of up to 1:9 [8], whereas the reaction catalyzed by bisoxazoline-copper(II) complexes gives a nearly 1:1 ratio of **6**:**7** [9] and **6** is the major product when a BINOL-aluminum(III) catalyst is used (Scheme 4.5) [10].



Scheme 4.5

The mechanism of the reaction of ethyl glyoxylate **4** with 2,3-dimethyl-1,3-butadiene **5** leading to the ene product **7** is shown in Scheme 4.5. This brief introduction to the reaction mechanism for cycloaddition reactions of carbonyl compounds activated by Lewis acids indicates that many factors influence the course of the reaction.

4.3
Cycloaddition Reactions of Carbonyl Compounds

The $[_{\pi}2+_{\pi}4]$-cycloaddition reaction of aldehydes and ketones with 1,3-dienes is a well-established synthetic procedure for the preparation of dihydropyrans which are attractive substrates for the synthesis of carbohydrates and other natural products [2]. Carbonyl compounds are usually of limited reactivity in cycloaddition reactions with dienes, because only electron-deficient carbonyl groups, as in glyoxylates, chloral, ketomalonate, 1,2,3-triketones, and related compounds, react with dienes which have electron-donating groups. The use of Lewis acids as catalysts for cycloaddition reactions of carbonyl compounds has, however, led to a new era for this class of reactions in synthetic organic chemistry. In particular, the application of chiral Lewis acid catalysts has provided new opportunities for enantioselective cycloadditions of carbonyl compounds.

4.3.1
Reactions of Unactivated Aldehydes

Some of the developments of catalytic enantioselective cycloaddition reactions of carbonyl compounds have origin in Diels-Alder chemistry, where many of the catalysts have been applied. This is valid for catalysts which enable monodentate coordination of the carbonyl functionality, such as the chiral aluminum and boron complexes. New chiral catalysts for cycloaddition reactions of carbonyl compounds have, however, also been developed.

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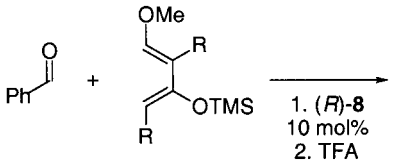
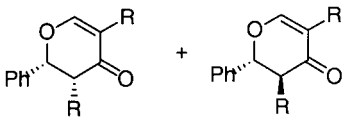
4.3.1.1 Chiral Aluminum and Boron Complexes

Yamamoto et al. were probably the first to report that chiral aluminum(III) catalysts are effective in the cycloaddition reactions of aldehydes [11]. The use of chiral BINOL-AlMe complexes (*R*)-**8** was found to be highly effective in the cycloaddition reaction of a variety of aldehydes with activated Danishefsky-type dienes. The reaction of benzaldehyde **1a** with Danishefsky's diene **2a** and *trans*-1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-pentadiene **2b** affords *cis* dihydropyrones, *cis*-**3**, as the major product in high yield with up to 97% ee (Scheme 4.6). The choice of the bulky triarylsilyl moiety in catalyst (*R*)-**8b** is crucial for high yield and the enantioselectivity of the reaction; in contrast with this the catalysts derived from $AlMe_3$ and (*R*)-3,3′-disubstituted binaphthol (substituent = H, Me, Ph) were effective in stoichiometric amounts only and were less satisfactory with regard to reactivity and enantioselectivity.

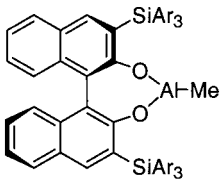
For the cycloaddition reaction in Scheme 4.6 it was found that 3-bromocamphor, for example, can bind selectively to one enantiomer of the complex [12] and that if the reaction was performed in the presence of the racemic catalyst **8** and 3-bromocamphor, *cis*-**3** was isolated with up to 80% ee compared to 95% ee for the reaction catalyzed by (*R*)-**8b**.



1a **2**
a: R = H
b: R = Me



	cis-**3** yield/ee (%)	*trans*-**3** yield (%)
2a, (*R*)-**8a**	71/67	-
2a, (*R*)-**8b**	81/81	-
2b, (*R*)-**8a**	77/95	7
2b, (*R*)-**8b**	90/97	3

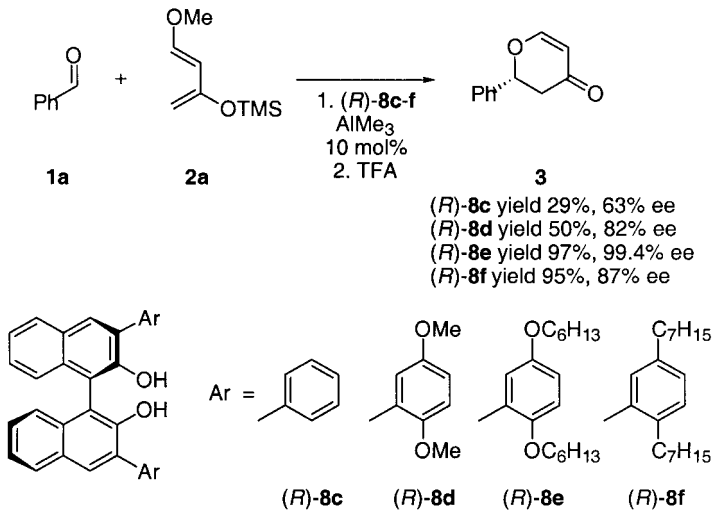


(*R*)-**8**
a: Ar = Ph
b: Ar = 3,5-xylyl

Scheme 4.6

The use of chiral BINOL-AlMe catalysts for the cycloaddition reactions has also included ligands which have the possibility of forming hypercoordinated aluminum complexes [13]. Performing the reaction of benzaldehyde **1a** with Danishefsky's diene **2a** gave the cycloaddition product **3** in the presence of (*R*)-**8c**-(*R*)-**8f** as the catalyst in up to 97% yield and 99.4% ee using (*R*)-**8e** as the catalyst (Scheme 4.7). A clear trend appears – ligand (*R*)-**8c**, which has neither the steric bulk nor the coordinating ether oxygen atoms characteristic of (*R*)-**8e**, catalyzes the reaction, but only modest yield and ee of **3** are obtained. Ligand (*R*)-**8d**, having methoxy groups, is almost as efficient as (*R*)-**8e**, but with a modest chemical yield. Ligand (*R*)-**8f**, which should be expected to have steric properties similar to those of (*R*)-**8e**, fell somewhere between (*R*)-**8c** and (*R*)-**8e** with 87% ee. The lack of the ether oxygen atoms in **8c** capable of coordinating to the metal significantly affects the enantioselectivity compared with (*R*)-**8e** and (*R*)-**8d**.

On the basis of the absolute configuration of the cycloaddition product **4**, formed in the reaction catalyzed by (*R*)-**8e**, model calculations using (*R*)-**8d** show that the preferred geometry for the intermediate is one in which the two oxygen



Scheme 4.7

atoms from the BINOL ligand and the methyl substituent are located in the equatorial plane with one of the ligand hypercoordinating ether oxygen atoms and the benzaldehyde oxygen atom as the two axial ligands, as shown in Scheme 4.8 [13]. The 2,5-dimethoxyphenyl substituent which is not coordinating to aluminum is oriented perpendicular to the BINOL ligand, whereas the 2,5-dimethoxyphenyl substituent which hypercoordinates to aluminum is twisted towards the metal. This twisting creates a chiral environment as the non-hypercoordinated 2,5-dimethoxyphenyl substituent shields the *si* face of benzaldehyde while the *re* face is available for approach by the diene.

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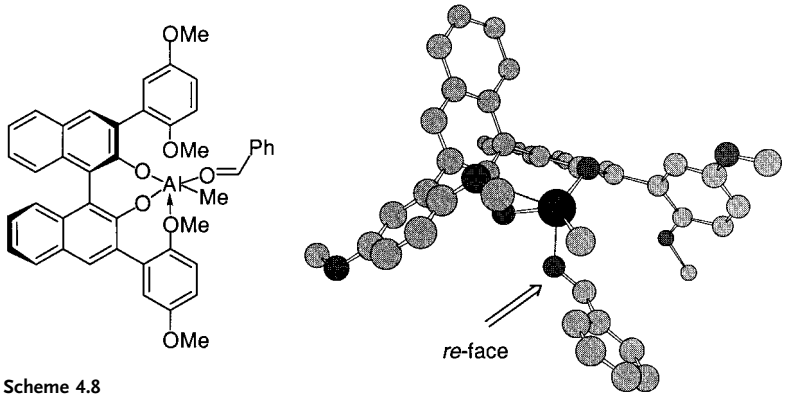


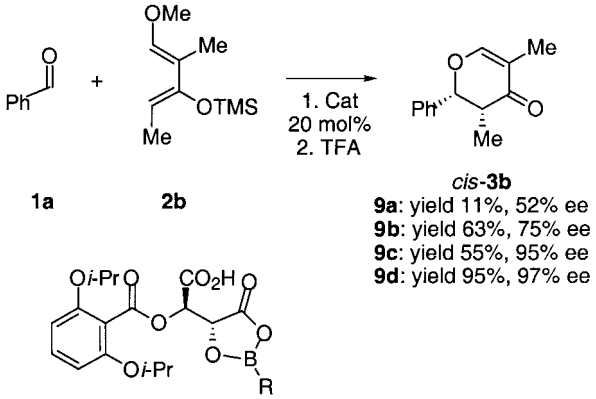
Scheme 4.8

The mechanism of the cycloaddition reaction of benzaldehyde **2a** with Danishefsky's diene **3a** catalyzed by aluminum complexes has been investigated theoretically using semi-empirical calculations [14]. It was found that the reaction proceeds as a step-wise cycloaddition reaction with the first step being a nucleophilic-like attack of Danishefsky's diene **2a** on the coordinated carbonyl compound leading to an aldol-like intermediate which is stabilized by interaction of the cation with the oxygen atom of the Lewis acid. The next step is the ring-closure step, giving the cycloaddition product.

A series of chiral binaphthyl ligands in combination with $AlMe_3$ has been used for the cycloaddition reaction of enamide aldehydes with Danishefsky's diene for the enantioselective synthesis of a chiral amino dihydroxy molecule [15]. The cycloaddition reaction, which was found to proceed via a Mukaiyama aldol condensation followed by a cyclization, gives the cycloaddition product in up to 60% yield and 78% ee.

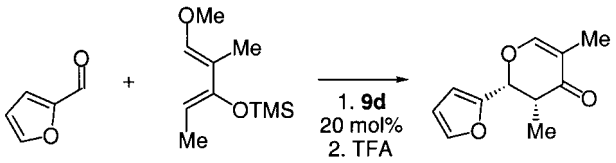
It should also be noted that chiral menthoxydichloroaluminum complexes can catalyze the cycloaddition reaction of carbonyl compounds but only small ee have been obtained [16].

Chiral boron(III) Lewis acid catalysts have also been used for enantioselective cycloaddition reactions of carbonyl compounds [17]. The chiral acyloxylborane catalysts **9a–9d**, which are also efficient catalysts for asymmetric Diels-Alder reactions [17, 18], can also catalyze highly enantioselective cycloaddition reactions of aldehydes with activated dienes. The arylboron catalysts **9b–9c** which are air- and moisture-stable have been shown by Yamamoto et al. to induce excellent chiral induction in the cycloaddition reaction between, e.g., benzaldehyde and Danishefsky's dienes such as **2b** with up to 95% yield and 97% ee of the cycloaddition product *cis*-**3b** (Scheme 4.9) [17].



Scheme 4.9

The cycloaddition reaction catalyzed by complex **9d** proceeds well for several aromatic and α,β-unsaturated aldehydes and has been used in an enantioselective route to the carbon-branched pyranose derivative *cis*-**3c** (Scheme 4.10) [17].



1b **2b** *cis*-**3c**
yield 98%, >99% ee

Scheme 4.10

A series of chiral boron catalysts prepared from, e.g., *N*-sulfonyl α-amino acids has also been developed and used in a variety of cycloaddition reactions [18]. Corey et al. have applied the chiral (*S*)-tryptophan-derived oxazaborolidine-boron catalyst **11** and used it for the conversion of, e.g., benzaldehyde **1a** to the cycloaddition product **3a** by reaction with Danishefsky's diene **2a** [18h]. This reaction **1a** affords mainly the Mukaiyama aldol product **10**, which, after isolation, was converted to **3a** by treatment with TFA (Scheme 4.11). It was observed that no cycloaddition product was produced in the initial step, providing evidence for the two-step process.

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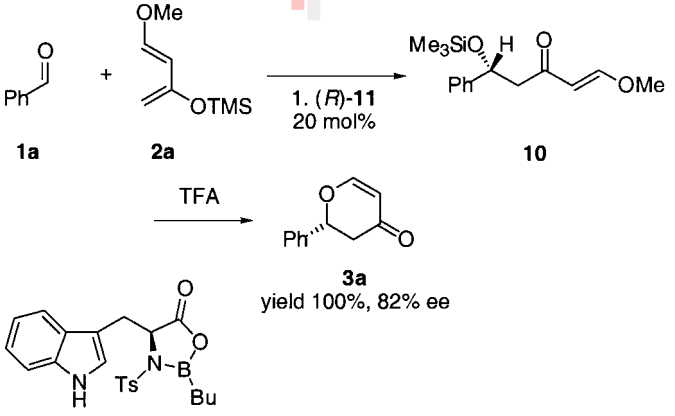


1a **2a** **10**

3a
yield 100%, 82% ee

11

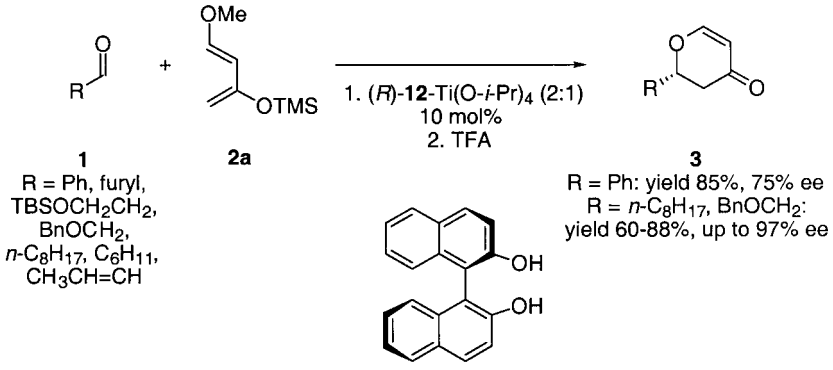
Scheme 4.11

4.3.1.2 **Chiral Transition- and Lanthanide-metal Complexes**

Different chiral transition- and lanthanide-metal complexes can catalyze the cycloaddition reaction of unactivated and activated aldehydes with especially activated

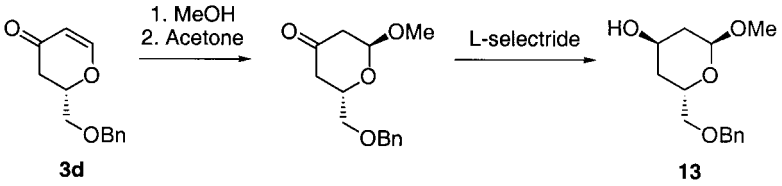
dienes. For the chiral titanium catalysts the focus has been on the use of mainly BINOL-titanium(IV) complexes for cycloaddition reactions. These catalysts have been widely used as chiral catalysts in enantioselective C–C bond-forming reactions of aldehydes [8, 19].

Keck et al. reported that a catalyst generated from (*S*)- or (*R*)-BINOL **12** and Ti(O-*i*-Pr)$_4$ in a 2:1 ratio is more selective than the catalyst formed from a 1:1 mixture [19f]. The former catalyst was shown to catalyze the cycloaddition reaction of aldehydes **1** with Danishefsky's diene **2a** affording the dihydropyrones **3** with moderate to excellent enantioselectivity (Scheme 4.12). The reaction proceeds well for different aldehydes with up to 97% ee and good yield of the cycloaddition products.



Scheme 4.12

The dihydropyrones are not produced directly in the initial BINOL-titanium(IV)-catalyzed reaction. The major product at this stage is the Mukaiyama aldol product which is subsequently cyclized by treatment with TFA [19f]. The formal cycloaddition product **3d** (97% ee) obtained from α-(benzyloxy)acetaldehyde is an important intermediate for compactin and mevinolin. Scheme 4.13 outlines how the structural subunit **13** is available in three steps via this cycloaddition approach [19f].



Scheme 4.13

The chiral BINOL/Ti(O-*i*-Pr)$_4$ combination has also been used as a very enantioselective catalyst for the cyclocondensation of polyfluoroalkylaldehydes with Danishefsky's diene leading to polyfluoroalkyldihydropyrenones in moderate yields (35–60%) and with high ee (90–98.5% ee) [20].

A chiral vanadium complex, bis(3-(heptafluorobutyryl)camphorato)oxovanadium(IV), can catalyze the cycloaddition reaction of, mainly, benzaldehyde with dienes of the Danishefsky type with moderate to good enantioselectivity [21]. A thorough investigation was performed with benzaldehyde and different activated dienes, and reactions involving double stereo differentiation using a chiral aldehyde.

Chiral salen chromium and cobalt complexes have been shown by Jacobsen et al. to catalyze an enantioselective cycloaddition reaction of carbonyl compounds with dienes [22]. The cycloaddition reaction of different aldehydes **1** containing aromatic, aliphatic, and conjugated substituents with Danishefsky's diene **2a** catalyzed by the chiral salen-chromium(III) complexes **14a**,**b** proceeds in up to 98% yield and with moderate to high ee (Scheme 4.14). It was found that the presence of oven-dried powdered 4 Å molecular sieves led to increased yield and enantioselectivity. The lowest ee (62% ee, catalyst **14b**) was obtained for hexanal and the highest (93% ee, catalyst **14a**) was obtained for cyclohexyl aldehyde. The mechanism of the cycloaddition reaction was investigated in terms of a traditional cycloaddition, or formation of the cycloaddition product via a Mukaiyama aldol-reaction path. In the presence of the chiral salen–chromium(III) catalyst system ^{1}H NMR spectroscopy of the crude reaction mixture of the reaction of benzaldehyde with Danishefsky's diene revealed the exclusive presence of the cycloaddition-pathway product. The Mukaiyama aldol condensation product was prepared independently and subjected to the conditions of the chiral salen-chromium(III)-catalyzed reactions. No detectable cycloaddition product could be observed. These results point towards a [2+4]-cycloaddition mechanism.

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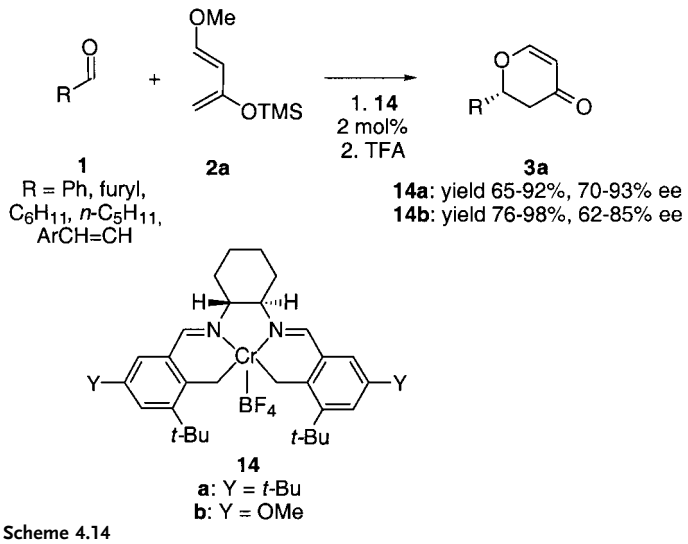
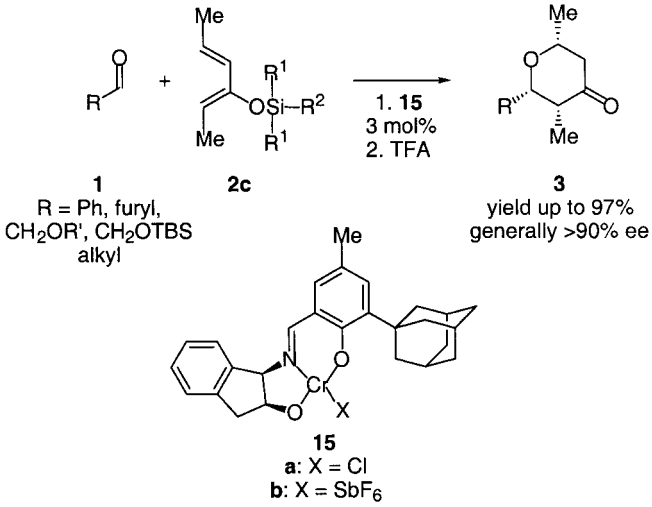


Scheme 4.14

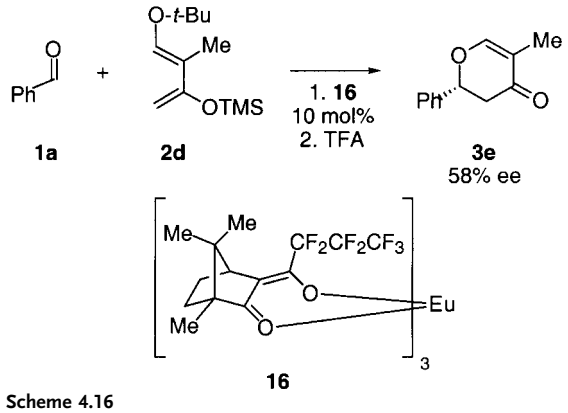
Jacobsen et al. took an important step towards the development of a more general catalytic enantioselective cycloaddition reaction of carbonyl compounds by introducing chiral tridentate Schiff base chromium(III) complexes **15** (Scheme 4.15) [23]. These complexes are highly diastereo- and enantioselective catalysts for the reaction of unactivated aldehydes and can catalyze the reaction of less nucleophilic dienes. The adamantyl-substituted catalysts **15a**,**b** gave the best results and both aliphatic and aromatic aldehydes underwent cycloaddition reactions; it was found that the use of catalyst **15b** resulted in a faster and more enantioselective reaction and that the reaction can proceed in the absence of solvent. The reaction was tested for a variety of dienes, e.g. 1-methoxy-1,3-butadiene reacts with $TBSOCH_2CHO$ in the presence of only 0.5 mol% catalyst **15a** to give the corresponding cycloaddition product in >99% ee. This latter reaction provides, after hydrolysis and oxidation to the corresponding lactone, efficient access to interesting natural product structures.



Scheme 4.15

Danishefsky et al. were probably the first to observe that lanthanide complexes can catalyze the cycloaddition reaction of aldehydes with activated dienes [24]. The reaction of benzaldehyde **1a** with activated conjugated dienes such as **2d** was found to be catalyzed by $Eu(hfc)_3$ **16** giving up to 58% ee (Scheme 4.16). The ee of the cycloaddition products for other substrates was in the range 20–40% with 1 mol% loading of **16**. Catalyst **16** has also been used for diastereoselective cycloaddition reactions using chiral *O*-menthoxy-activated dienes derived from (–)-menthol, giving up to 84% de [24b,c]; it has also been used for the synthesis of optically pure saccharides.

It has been shown that ytterbium tris-(*R*)-(–)-1,1′-binaphthyl-2,2′-diyl phosphonate can catalyze the reaction of aromatic aldehydes with Danishefsky's diene to



Scheme 4.16

give the cycloaddition product in good yield and with up to 93% ee [25]. It was found that 2,6-lutidine can improve the catalytic properties.

4.3.2 Reactions of Activated Aldehydes

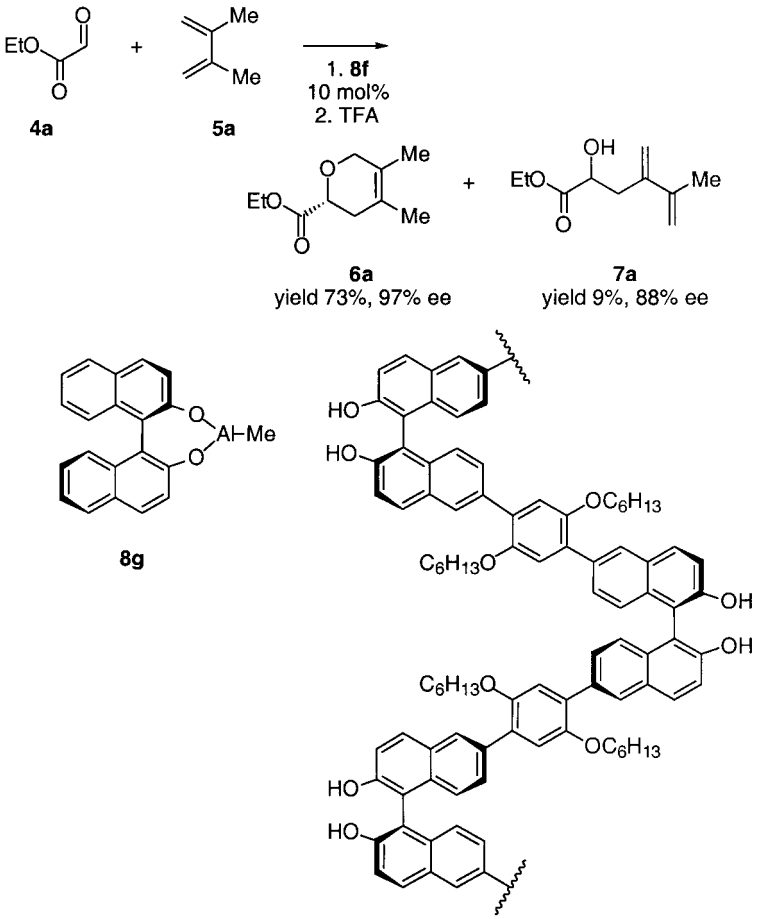
Different main-group-, transition- and lanthanide-metal complexes can catalyze the cycloaddition reaction of activated aldehydes with activated and non-activated dienes. The chiral metal complexes which can catalyze these reactions include complexes which enable substrates to coordinate in a mono- or bidentate fashion.

DropBooks

4.3.2.1 Chiral Aluminum and Boron Complexes

Chiral BINOL-AlMe complexes can catalyze a highly chemo- and enantioselective cycloaddition reaction of activated aldehydes with conjugated dienes [10]. The reaction of ethyl glyoxylate **4a** with, e.g., 2,3-dimethyl-1,3-butadiene **5a**, in the presence of (*R*)-BINOL-AlMe **8g** as the catalyst, gives **6a** as the major product in 73% yield with up to 97% ee and 7% of the ene product **7a** (Scheme 4.17). Chiral polymer Lewis acid complexes can also be used as catalysts for the reaction in Scheme 4.17 [26]. The use of the chiral polybinaphthyl polymer **17** in combination with $AlMe_3$ in the reaction of **4a** with **5a** gave **6a** in 67% yield and up to 95% ee. The most important aspect of the using **17** is that it can easily be recovered by simple filtration and reused without significant change in yield or chemo- or enantioselectivity.

Chiral boron(III) complexes can catalyze the cycloaddition reaction of glyoxylates with Danishefsky's diene (Scheme 4.18) [27]. Two classes of chiral boron catalyst were tested, the *β*-amino alcohol-derived complex **18** and bis-sulfonamide complexes. The former catalyst gave the best results for the reaction of methyl glyoxylate **4b** with diene **2a**; the cycloaddition product **6b** was isolated in 69% yield and 94% ee, while the chiral bis-sulfonamide boron complex resulted in only

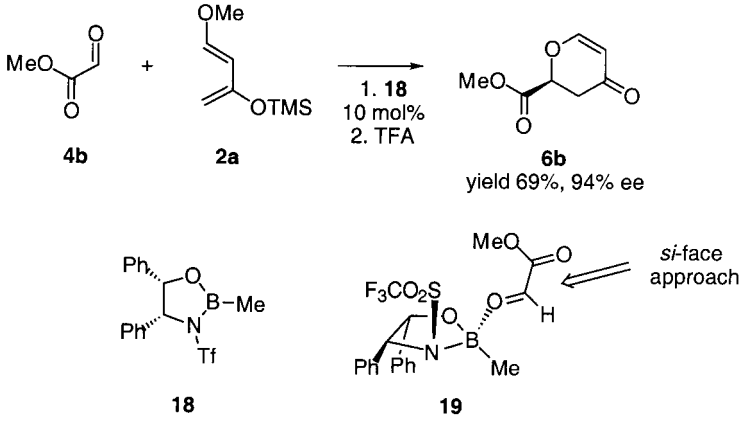


Scheme 4.17

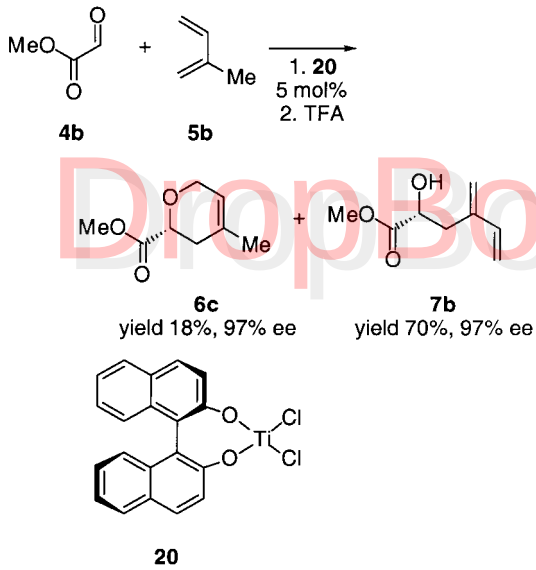
62% ee. On the basis of the absolute configuration of **6b** it was postulated that **4b** coordinates in a monodentate fashion to **18** as outlined in **19**, in which the *re* face of the activated carbonyl functionality is shielded by the triflate group, enabling the diene to approach in an *endo* fashion to the *re* face of the carbonyl functionality [27].

The interest in chiral titanium(IV) complexes as catalysts for reactions of carbonyl compounds has, e.g., been the application of BINOL-titanium(IV) complexes for ene reactions [8, 19]. In the field of catalytic enantioselective cycloaddition reactions, methyl glyoxylate **4b** reacts with isoprene **5b** catalyzed by BINOL-TiX_2 **20** to give the cycloaddition product **6c** and the ene product **7b** in 1:4 ratio; enantioselectivity is excellent – 97% ee for the cycloaddition product (Scheme 4.19) [28].

It has also been shown by Mikami et al. that a BINOL-titanium(IV) complex in which the 6,6′ position of the BINOL ligand is substituted with bromine catalyzes



Scheme 4.18



DropBooks

Scheme 4.19

a selective cycloaddition reaction of methyl glyoxylate with 1-methoxy-1,3-diene in up to 81% yield and 97% ee [28c].

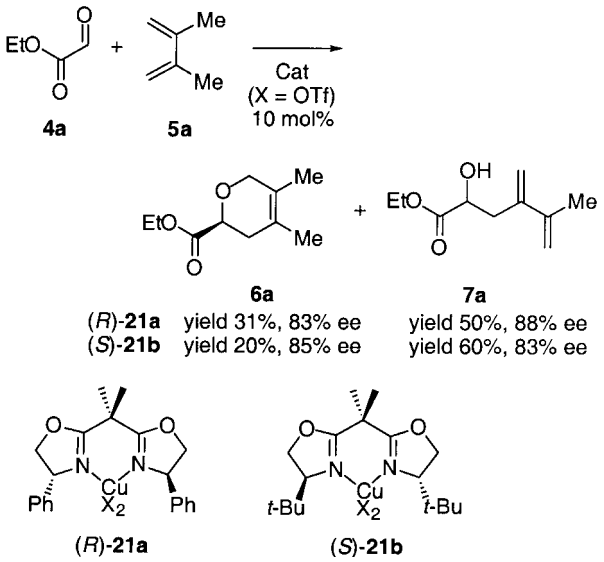
A remarkable change in reaction course is notable when changing the metal from aluminum to titanium for cycloaddition reactions using BINOL as the chiral ligand. When the chiral aluminum(III) catalyst is applied the cycloaddition product is the major product, whereas for the chiral titanium(IV) catalyst, the ene product is the major product. The reason for this significant change in reaction course is not fully understood. Maybe the glyoxylate coordinates to the former Le-

wis acid complex in a monodentate fashion, whereas in the latter reaction the glyoxylate coordinates in a bidentate fashion, and these two coordination modes promote the two different reaction courses.

Chiral salen-cobalt(III) complexes can also catalyze the reaction of glyoxylates with activated dienes to give the cycloaddition product in moderate yield and ee [29].

Chiral C_2-symmetric bisoxazoline-copper(II) complexes [30, 31] were introduced as catalysts for cycloaddition and ene reactions of glyoxylates with dienes [9] leading to intense activity in the use of these catalyst for different cycloaddition reactions.

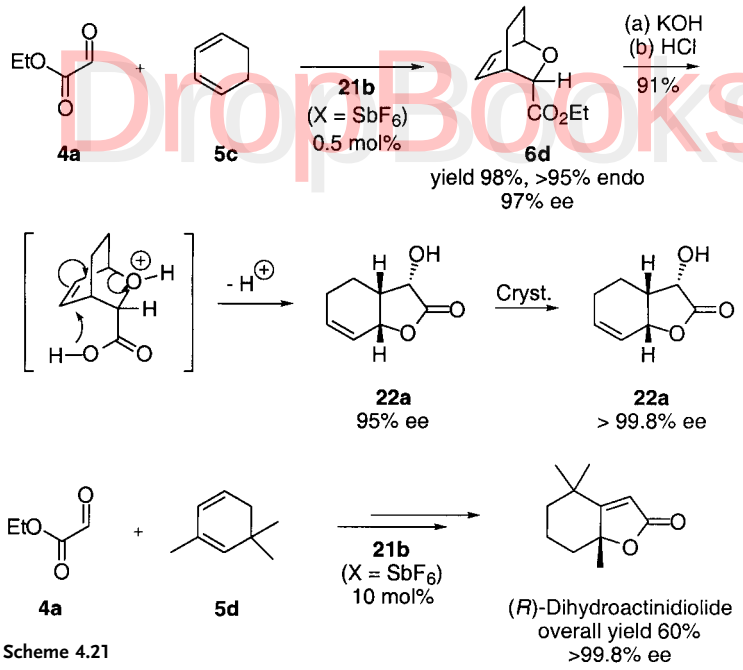
For the reaction of ethyl glyoxylate **4a** with, e.g., 2,3-dimethyl-1,3-butadiene **5a** in the presence of Ph-BOX-CuX_2 (*R*)-**21a** and *t*-Bu-BOX-CuX_2 (*S*)-**21b** catalysts (BOX = bisoxazoline) a nearly 1:2 ratio of the cycloaddition product **6a** relative to the ene product **7b** were obtained (Scheme 4.20). The absolute configuration of the product in these cycloaddition reactions catalyzed by the chiral BOX-copper(II) complexes led to the observation that the 4-*tert*-butyl-BOX ligand and the 4-phenyl-BOX ligand in combination with copper(II) salts give opposite asymmetric induction in the product. Using the copper catalysts derived from the *R* enantiomer of the phenyl-BOX ligand and the *S* enantiomer of the *tert*-butyl-BOX ligand in combination with copper(II) afforded the same *S* enantiomer of the cycloaddition product.



Scheme 4.20

The enantioselective cycloaddition reaction catalyzed by chiral BOX-copper(II) complexes has been used for conjugated cyclic dienes, e.g. 1,3-cyclohexadiene **5c**, as shown in Scheme 4.21 [9, 32]. This cycloaddition reaction is dependent on sol-

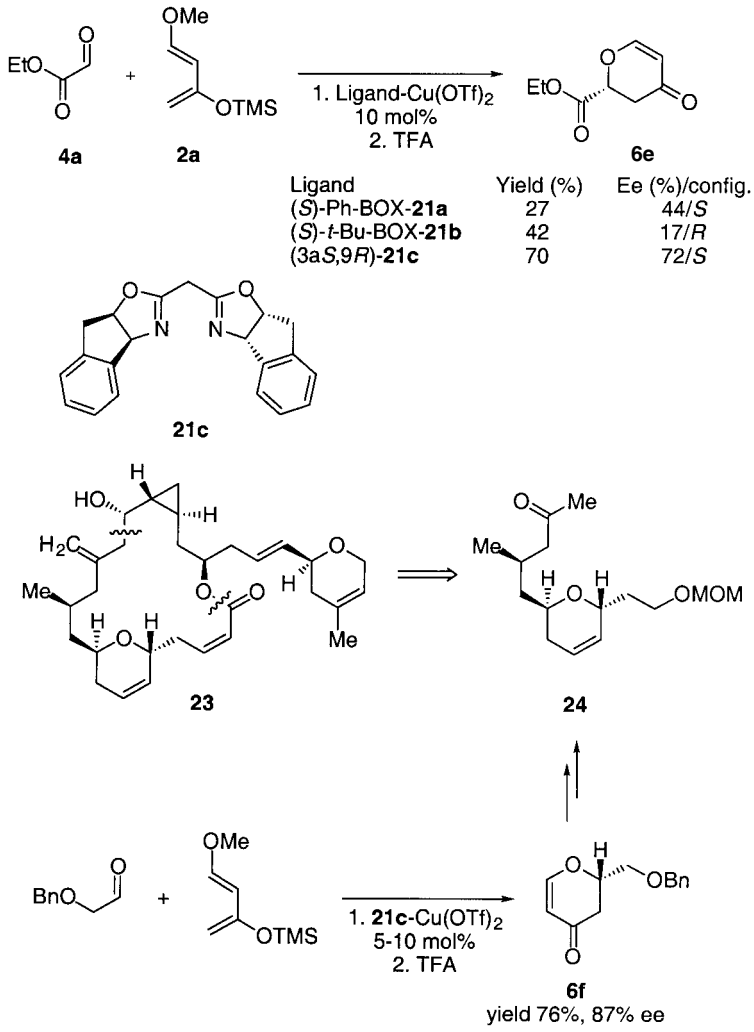
vent, and counter-ions have been found to have significant effects on the rate and enantioselectivity of this reaction [32]. A much faster reaction for **5c** was observed using less coordinating antimonate instead of triflate as the counter-ion, and carrying out the reaction in a more polar solvent, e.g. $MeNO_2$ instead of CH_2Cl_2, under which conditions the cycloaddition product **6d** was isolated in 98% yield with >97% ee (Scheme 4.21). It was rationalized that the reactive BOX-copper(II) catalyst is a dicationic species. Therefore, the dissociation of the two counter-ions from copper is important to activate the catalyst, and the more polar solvents will stabilize the dissociated ligand-copper cations. The potential of this reaction is illustrated by the enantioselective synthesis of a bicyclic lactone **22a** by treatment with base followed by a rearrangement reaction under acidic conditions (Scheme 4.21). This approach has been used for the synthesis of (*R*)-dihydroactinidiolide (Scheme 4.21) [33], one of the main components of the pheromone for queen recognition of the workers of the red fire ant, *Soleneopsis invicta*. The crucial step in this total synthesis is the catalytic enantioselective cycloaddition reaction of ethyl glyoxylate **4a** with 2,6,6-trimethyl-1,3-cyclohexadiene **5d** giving a highly regio, diastereo- and enantioselective reaction by application of (*S*)-*t*-Bu-BOX-CuX_2 (X = SbF_6) **21b** as the catalyst.



Scheme 4.21

The cycloaddition reaction between ethyl glyoxylate **4a** and Danishefsky's diene **2a** has been investigated by Ghosh et al. applying catalyst systems derived from $Cu(OTf)_2$ and ligands (*S*)-Ph-BOX (*S*)-**21a**, (*S*)-*t*-Bu-BOX (*S*)-**21b**, and the confor-

mationally constrained BOX ligand **21c** to compare the properties of the last ligand with the two others (Scheme 4.22) [34]. An ee of 72% and 70% yield of the cycloaddition product **6e** were obtained using **21c**-Cu(OTf)$_2$, which for this particular reaction was a significant improvement compared with the two other catalysts. This methodology has been used for the synthesis of the C_3–C_{14} segment **24** of the antitumor agent laulimalide **23** (Scheme 4.22) [35]. The constrained chiral BOX ligand **21c** in combination with Cu(OTf)$_2$ afforded dihydropyrane **6f** by a cycloaddition reaction in good yield and ee; this was converted to the C_3–C_{14} segment **24** via a Ferrier-type rearrangement in several steps.



Scheme 4.22

Chiral BOX-zinc(II) complexes can also catalyze the cycloaddition reaction of glyoxylates with, e.g., 2,3-dimethyl-1,3-butadiene and 1,3-cyclohexadiene [36]. The reaction gave for the former diene a higher cycloaddition product/ene product ratio compared with the corresponding chiral copper(II) complexes; the ee, however, was slightly reduced. For the reaction of 1,3-cyclohexadiene slightly lower yield and ee were also found.

Desimoni et al. have found that chiral BOX-manganese(II) complexes can catalyze the intramolecular cycloaddition and ene reactions, with the latter as the major product [37].

The mechanism of, and especially the intermediate in, the cycloaddition reactions catalyzed by the chiral BOX-copper(II) complexes have received considerable attention because of the peculiar ligand effect on the asymmetric induction. On the basis of absolute configuration of the cycloaddition products obtained in the reaction of ethyl glyoxylate with conjugated dienes it was proposed that two different intermediates were operating, depending on the substituent attached to the chiral center in the BOX ligand [9]. It has been proposed that these two intermediates are tetrahedral (Scheme 4.23, **25**) in which glyoxylate is coordinated to (*S*)-Ph-BOX-Cu(II) in a bidentate fashion, whereas a square-planar intermediate (Scheme 4.23, **26**) could account for the absolute configuration of the cycloaddition products obtained in reactions catalyzed by (*S*)-*t*-Bu-BOX-Cu(II). The two different structural intermediates **25** and **26** enable the diene to approach the same face of the carbonyl functionality leading to the same absolute configuration in the product, although the absolute configuration of the chiral ligand is opposite.

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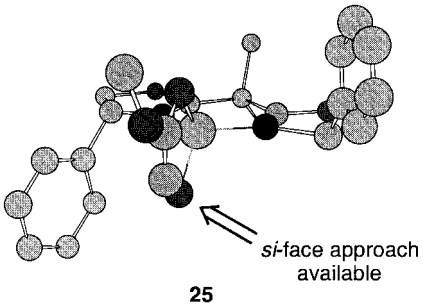
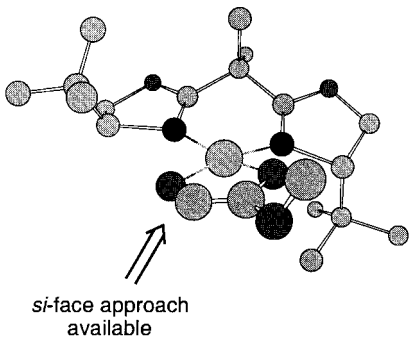
Several chiral BOX-copper(II) catalysts **27a–c**, **28a**,**b** [31h, 38] and chiral BOX-copper(II) substrate/hydrolyzed enone complexes **29a**,**b** [31f, 39] have been characterized by X-ray structure analysis (Scheme 4.24).

Chiral BOX-copper(II)-coordinated complexes can have different coordination geometries. When the coordination number is four copper(II) has distorted square-planar geometry with a dihedral angle θ in the range from $\theta = +7.0^\circ$ for the *i*-Pr-BOX-Cu$(OH_2)_2$ complex **27a** to $\theta = +33.3^\circ$ for *t*-Bu-BOX-Cu$(OH_2)_2$ **27b** and $\theta = -9.3^\circ$ for Ph-BOX-Cu$(OH_2)_2$ **27c** [38a]. When the coordination number is five the complex has square-pyramidal geometry **28a** with the water molecules distorted 26° out of the plane [38b]. For the (*S*)-Ph-BOX-Cu$(OTf)_2(OH_2)_2$ complex, an octahedral complex is found **28b** [31h]. A chiral BOX-copper(II)-alkylidene malonate complex has a distorted square-planar geometry with an average distortion of 26° **29a** [31f]. In the inverse electron-demand cycloaddition reaction catalyzed by (*S*)-**21b**, a failed reaction with an enone gave a crystal of the anion of the hydrolyzed enone bound to the chiral BOX-copper(II) **29b**, in which the average distortion of the two oxygen atoms was 23° [39]. If it is assumed that glyoxylate replaces the two water molecules in **27b**, a chiral BOX-copper(II) substrate intermediate **25** is formed which can account for the experimentally observed stereochemical outcome of the reactions catalyzed by the *t*-Bu-BOX-Cu(II) and *i*-Pr-BOX-Cu(II) complexes. The structure of complexes **29a**,**b** also supports the distorted square-planar intermediate **25** for reactions catalyzed by the *t*-Bu-BOX-Cu(II) complexes. The X-ray structure of the (*S*)-Ph-BOX-Cu$(H_2O)_2 \cdot 2SbF_6$ complex **27c** can-



25



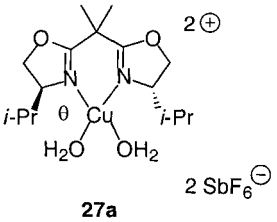
26

Scheme 4.23

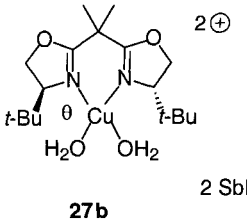
not, however, account for the absolute configuration of the cycloaddition products obtained by use of this catalyst, whereas the tetrahedral intermediate **26** does.

The above described X-ray structures were mainly obtained by Evans et al. They did not, however, propose any model that rationalizes the asymmetric induction by the Ph-BOX-Cu(II) catalyst in the original paper dealing with Diels-Alder reactions [40]. The same group recently published a paper concerning the opposite asymmetric induction of the catalysts Ph-BOX-Cu(II) and *t*-Bu-BOX-Cu(II) [38a]. Although they have not yet offered an explanation of this phenomenon, it was indicated that a tetrahedral copper(II) center was unlikely. The major arguments for this conclusion were the high *endo* selectivity observed from the cycloaddition and ene reactions catalyzed by Ph-BOX-Cu(II) and the lack of the obvious electronic effects from *para*-X-Ph-BOX ligands in combination with copper(II) salts. The ee of the product obtained in cycloaddition reactions using *para*-X-Ph-BOX ligands and copper(II) salts were: X=Cl: 89% ee; X=H: 93% ee; X=OMe: 93% ee. The unambiguous electronic effect of the *para* substituents on X-Ph-BOX ligands cannot exclude possible attractive catalyst-substrate (π-donor-π-acceptor) interactions. To account for the enantioselective induction in reactions catalyzed by *para*-X-Ph-BOX-Cu(II) Evans et al. proposed a square-pyramidal geometry [38a].

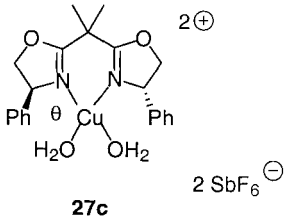
Cationic BINAP-palladium and platinum complexes **30a**,**b** can catalyze highly enantioselective cycloaddition reactions of arylglyoxals with acyclic and cyclic



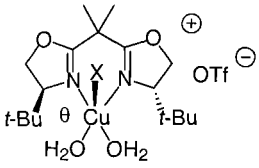
27a
distorted square planar geometry[38a]
θ = +7.0° (average)



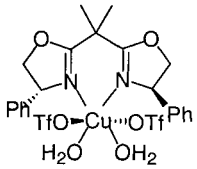
27b
distorted square planar geometry[38a]
θ = +33.3° (average)



27c
distorted square planar geometry[38a]
θ = -9.3° (average)



28a
X = OTf
square pyramidal geometry[38b]
θ = +26° (average)



28b
octahedral geometry[31h]

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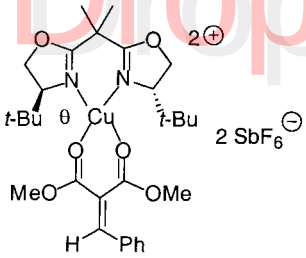
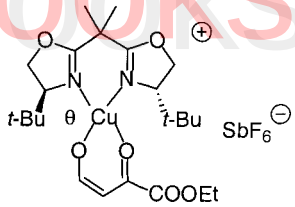


29a
distorted square planar geometry[31f]
θ = +11.8° (average)

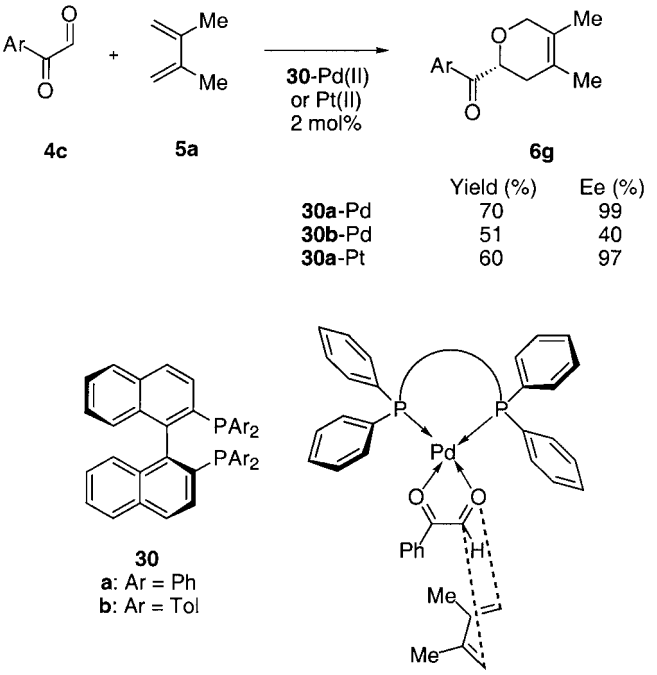


29b
distorted square planar geometry[39]
θ = +23° (average)

Scheme 4.24

dienes, as shown in Scheme 4.25 [41]. The cycloaddition reaction proceeds well for reaction of phenylglyoxal **4c** with 2,3-dimethyl-1,3-butadiene **5a** catalyzed by BINAP-Pd(II) and BINAP-Pt(II) giving 70% and 60% yield, and 99% and 97% ee, respectively, for the two catalysts. Enantioselective reactions catalyzed by **30a,b** proceed with no ene product formation for *para*-substituted arylglyoxals and lead to good yields and high ee for acyclic and cyclic dienes, e.g., 1,3-cyclohexadiene, which gives 69% and 74% yield and >99% ee of the *endo* diastereomer as the

only product for the two catalysts. When changing the dienophile to glyoxylate esters, the reaction with, e.g., 2,3-dimethyl-1,3-butadiene in the presence of **30a** as the catalyst gave almost equal amounts of the cycloaddition and ene products [41b]. The selectivity of the cycloaddition product was excellent, with up to 98% ee. On the basis of the X-ray structure of the cationic palladium species coordinated with an (*S*)-BINAP ligand with slightly distorted square-planar geometry, it was proposed that the two carbonyl atoms of the phenyl glyoxal coordinate to the metal in a bidentate fashion as shown for **31**. Because the approach of the diene to the *si* face of the formyl group is blocked by the equatorial phenyl group of the ligand, the diene attacks the *re* face to favor the observed (*R*) cyclo product [41b].

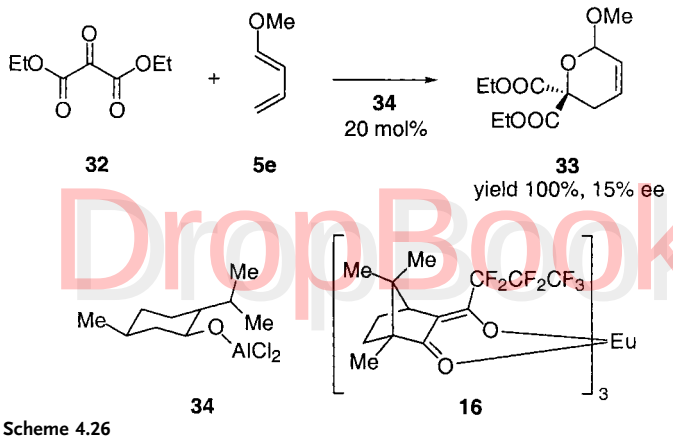


Scheme 4.25

Few investigations have included chiral lanthanide complexes as catalysts for cycloaddition reactions of activated aldehydes [42]. The reaction of *tert*-butyl glyoxylate with Danishefsky's diene gave the expected cycloaddition product in up to 88% yield and 66% ee when a chiral yttrium bis-trifluoromethanesulfonylamide complex was used as the catalyst.

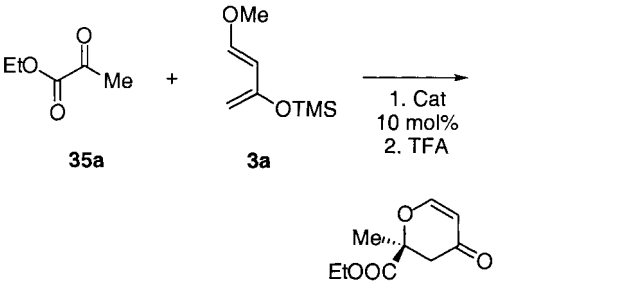
4.3.3
Reactions of Ketones

Because ketones are generally less reactive than aldehydes, cycloaddition reaction of ketones should be expected to be more difficult to achieve. This is well reflected in the few reported catalytic enantioselective cycloaddition reactions of ketones compared with the many successful examples on the enantioselective reaction of aldehydes. Before our investigations of catalytic enantioselective cycloaddition reactions of activated ketones [43] there was probably only one example reported of such a reaction by Jankowski et al. using the menthoxyaluminum catalyst **34** and the chiral lanthanide catalyst **16**, where the highest enantiomeric excess of the cycloaddition product **33** was 15% for the reaction of ketomalonate **32** with 1-methoxy-1,3-butadiene **5e** catalyzed by **34**, as outlined in Scheme 4.26 [16].



Scheme 4.26

The C_2-symmetric BOX-copper(II) complexes can also catalyze highly enantioselective cycloaddition reactions of α-keto esters and α-diketones with conjugated dienes [43]. Simple dienes, such as 2,3-dimethylbutadiene or 1,3-cyclohexadiene, do not react in a cycloaddition reaction with ethyl pyruvate **35a** in the presence of chiral BOX-copper(II) complexes. The use of Danishefsky's diene **2a**, however, afforded the cycloaddition reaction (Scheme 4.27). Many different chiral BOX ligands were tested and it was found that the *t*-Bu-BOX-CuX_2 **21b** catalyst is the best for the reaction shown in Scheme 4.27. The reaction is highly dependent on the counter-ions which have a significant effect on the yield and ee of the cycloaddition product **36a**; triflate is superior to antimonate for this reaction, because it led to higher yield and ee in all the examples studied. This contrasts with previous observations [32, 44], but the better results using triflate in the current reaction could be that the triflate provides the suitable Lewis acidity for activating the dienophile, and/or the fluoride atoms contained in the antimonate might destroy, or interfere with, with the silyloxy-containing diene.

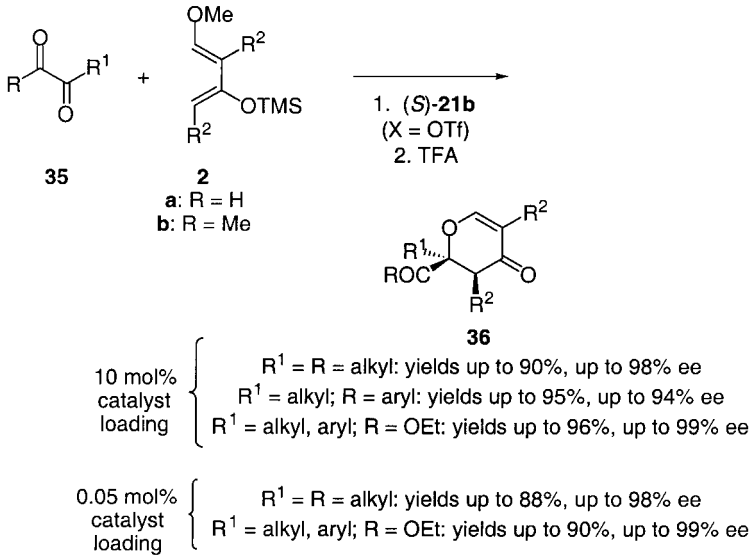


Scheme 4.27

The cycloaddition reaction of activated dienes catalyzed by *t*-Bu-BOX-Cu(II) (*S*)-**21b** is a reaction which can be used for different *α*-dicarbonyl compounds **35**. The results outlined in Scheme 4.28 shows the scope of the catalytic enantioselective reaction using 10 mol% of the catalyst. High yields and excellent ee of the cycloaddition products **36** were obtained in reactions of **35** with the activated dienes **2a,b**. The results also show that the reaction proceeds well with good yield and very high ee for *α*-diketones and *α*-keto esters containing alkyl and phenyl substituents. These cycloaddition reactions can proceed to complete conversion using only 0.05 mol% of the catalyst (*S*)-**21b** (X=OTf) with only one enantiomer detected by chiral GC of the crude product [43b]. The very low catalyst loading was found to be quite general for different *α*-dicarbonyl substrates and some representative results are also given in Scheme 4.28. The turn-over number for the reaction of methyl pyruvate with Danishefsky's diene is 1800/mol catalyst (based on 90% yield using 0.05 mol% of the catalyst) for 20 h, or 90 mol^{-1} h^{-1}. This is probably one of the lowest catalyst loadings, in addition to providing one of the highest turn-over numbers in Lewis acid-catalyzed enantioselective reactions.

The absolute configuration of the cycloaddition product obtained by the reaction of ketones with activated dienes catalyzed by (*S*)-*t*-Bu-BOX-Cu(II) (*S*)-**21b** points also to an intermediate in which the geometry around the central copper atom is square-planar similar to **26** above, and that the diene approaches the carbonyl functionality in an *endo* fashion.

The chiral BOX-metal(II) complexes can also catalyze cycloaddition reactions of other ketonic substrates [45]. The reaction of ethyl ketomalonate **37** with 1,3-conjugated dienes, e.g. 1,3-cyclohexadiene **5c** can occur with chiral BOX-copper(II) and zinc(II) complexes, Ph-BOX-Cu$(OTf)_2$ (*R*)-**21a**, and Ph-BOX-Zn$(OTf)_2$ (*R*)-**39**, as the catalysts (Scheme 4.29). The reaction proceeds with good yield and ee using the latter complex as the catalyst. Compared to the copper(II)-derived catalyst, which affects a much faster reaction, the use of the zinc(II)-derived catalyst is more convenient because the reaction gives 94% yield and 94% ee of the cycloaddition product **38**. The cycloaddition product **38** can be transformed into the optically active CO_2-


OMe
R2
OTMS
R2
1. (S)-21b
(X = OTf)
2. TFA
35
2
a: R = H
b: R = Me
R2
R1
ROC
O
O
R2
36
10 mol% catalyst loading
R1 = R = alkyl: yields up to 90%, up to 98% ee
R1 = alkyl; R = aryl: yields up to 95%, up to 94% ee
R1 = alkyl, aryl; R = OEt: yields up to 96%, up to 99% ee
0.05 mol% catalyst loading
R1 = R = alkyl: yields up to 88%, up to 98% ee
R1 = alkyl, aryl; R = OEt: yields up to 90%, up to 99% ee

Scheme 4.28

synthon **40** which might have potential in organic synthesis, because it can be converted into diol **41** (Scheme 4.29), a key intermediate for the synthesis of, e.g., cyclohexenyl carbinols and anticapsin.

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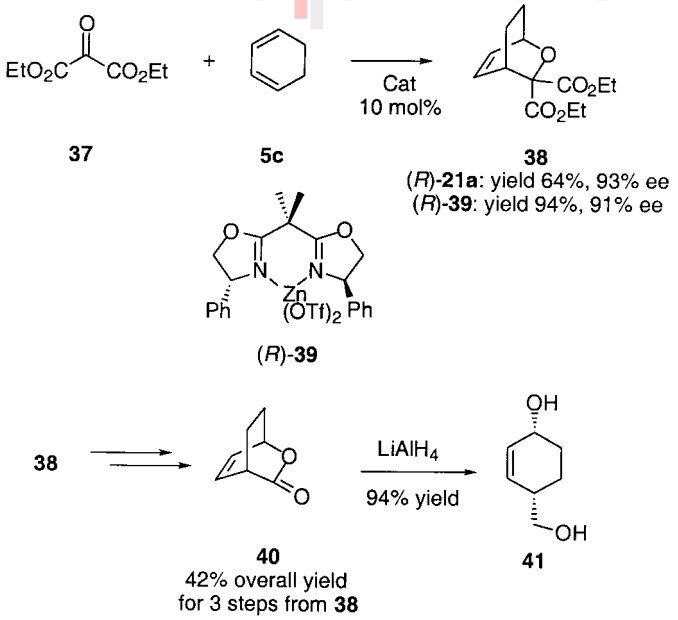
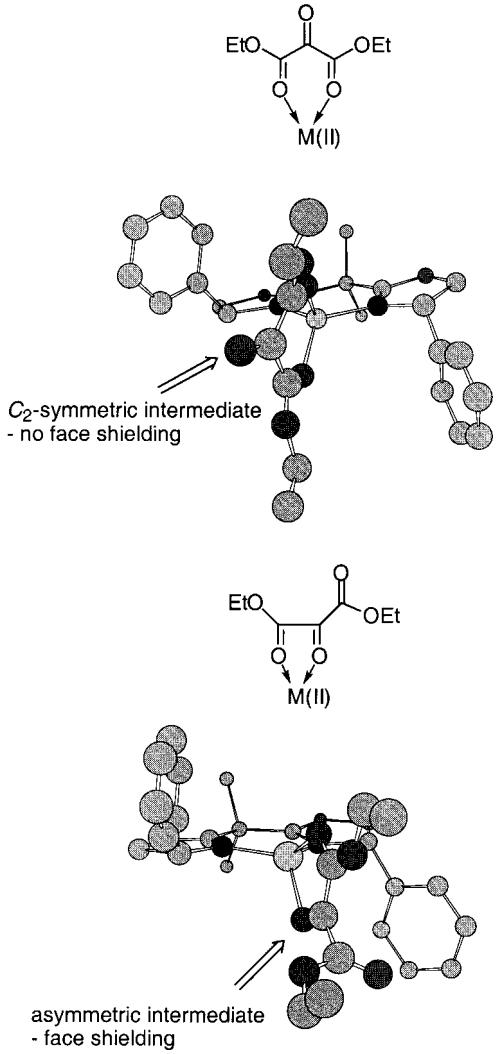


Scheme 4.29

To account for the course of this reaction theoretical calculations of the coordination of ketomalonate **37** to copper(II) and zinc(II) have revealed that the six-membered ring system is slightly more stable than the five-membered ring system (Scheme 4.30). The coordination of **37** to catalyst (*R*)-**39** shows that the six-membered intermediate is C_2-symmetric with no obvious face-shielding of the carbonyl functionality (top), while for the five-membered intermediate (bottom) the carbonyl is shielded by the phenyl substituent. Calculations of the transition-state energy for the reaction of the two intermediates with 1,3-cyclohexadiene leads to the lowest energy for the five-membered intermediate; this approach is in agreement with the experimental results [45].

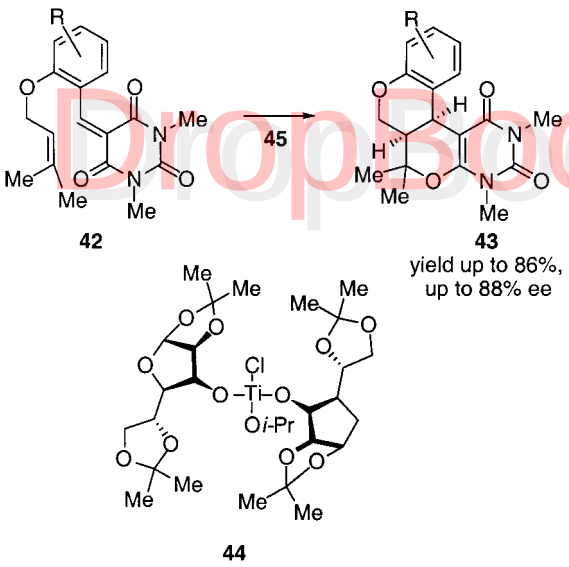


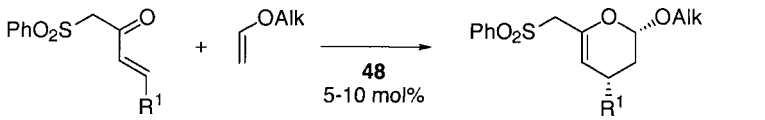
Scheme 4.30

4.3.4
Inverse Electron-demand Reactions

A simple approach for the formation of 2-substituted 3,4-dihydro-2*H*-pyrans, which are useful precursors for natural products such as optically active carbohydrates, is the catalytic enantioselective cycloaddition reaction of *α,β*-unsaturated carbonyl compounds with electron-rich alkenes. This is an inverse electron-demand cycloaddition reaction which is controlled by a dominant interaction between the LUMO of the 1-oxa-1,3-butadiene and the HOMO of the alkene (Scheme 4.2, right). This is usually a concerted non-synchronous reaction with retention of the configuration of the dienophile and results in normally high regioselectivity, which in the presence of Lewis acids is improved and, furthermore, also increases the reaction rate.

The inverse electron-demand catalytic enantioselective cycloaddition reaction has not been investigated to any great extent. Tietze et al. published the first example of this class of reaction in 1992 – an intramolecular cycloaddition of heterodiene **42** catalyzed by a diacetone glucose derived-titanium(IV) Lewis acid **44** to give the *cis* product **43** in good yield and up to 88% ee (Scheme 4.31) [46].

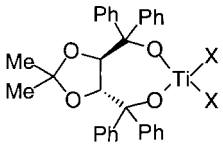

R
O
O
N
Me
Me
O
N
O
Me
Me
45
H
H
Me
Me
Me
Me
Cl
Ti
O
O
O



45a: R^1 = Me
45b: R^1 = *i*-Pr
45c: R^1 = Ph

46

47a: R^1 = Me, yield 90%, 97% ee
47b: R^1 = *i*-Pr, yield 88%, 86% ee
47c: R^1 = Ph, yield 77%, 97% ee



48
X = Cl, Br

Scheme 4.32

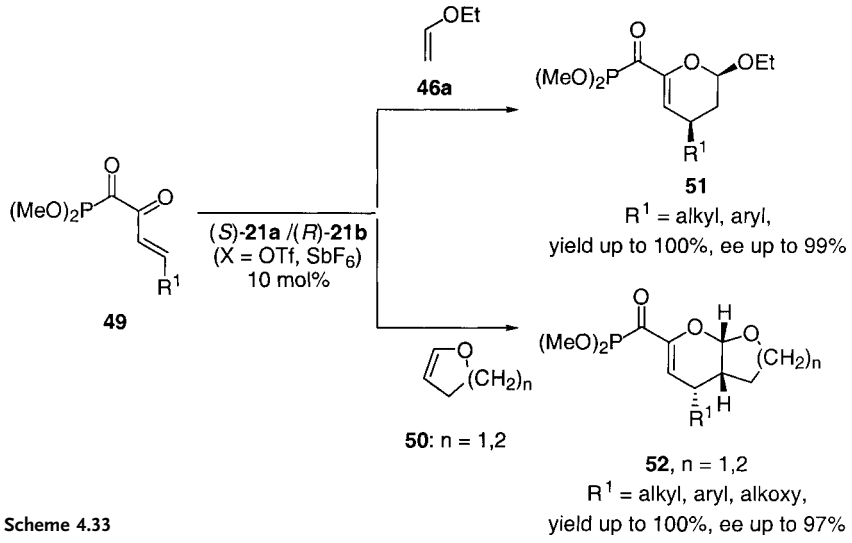
The chiral BOX-copper(II) complexes are effective catalysts for enantioselective cycloaddition reactions of α,β-unsaturated acyl phosphonates [48] and α,β-unsaturated keto esters [38b, 49].

The chiral BOX-copper(II) complexes, (*S*)-**21a** and (*R*)-**21b** (X=OTf, SbF_6), were found by Evans et al. to catalyze the enantioselective cycloaddition reactions of the α,β-unsaturated acyl phosphonates **49** with ethyl vinyl ether **46a** and the cyclic enol ethers **50** giving the cycloaddition products **51** and **52**, respectively, in very high yields and ee as outlined in Scheme 4.33 [38b]. It is notable that the acyclic and cyclic enol ethers react highly stereoselectively and that the same enantiomer is formed using (*S*)-**21a** and (*R*)-**21b** as the catalyst. It is, furthermore, of practical importance that the cycloaddition reaction can proceed in the presence of only 0.2 mol% (*R*)-**21a** (X=SbF_6) with minimal reduction in the yield of the cycloaddition product and no loss of enantioselectivity (93% ee).

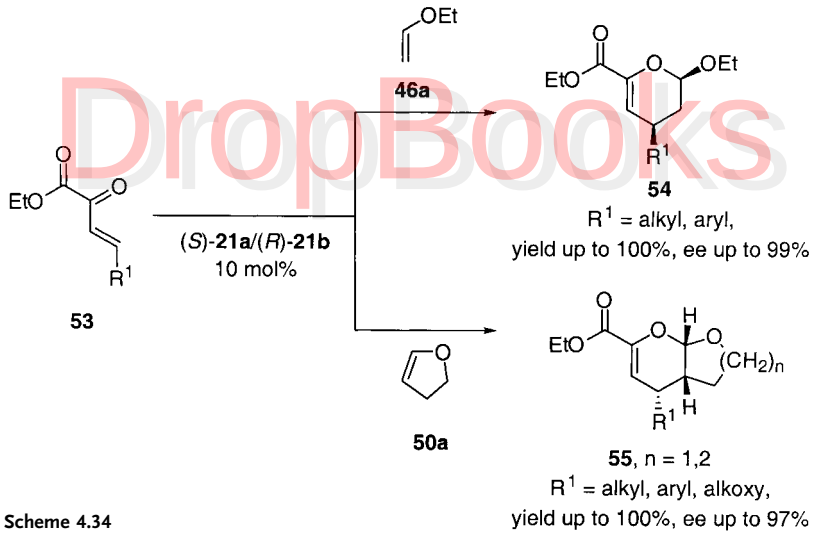
More recently, further developments have shown that the reaction outlined in Scheme 4.33 can also proceed for other alkenes, such as silyl-enol ethers of acetophenone [48b], which gives the *endo* diastereomer in up to 99% ee. It was also shown that β-ethyl-β-methyl-substituted acyl phosphonate also can undergo a diastereo- and enantioselective cycloaddition reaction with ethyl vinyl ether catalyzed by the chiral Ph-BOX-copper(II) catalyst. The preparative use of the cycloaddition reaction was demonstrated by performing reactions on the gram scale and showing that no special measures are required for the reaction and that the dihydropyrans can be obtained in high yield and with very high diastereo- and enantioselective excess.

Our development of the catalytic enantioselective inverse electron-demand cycloaddition reaction [49], which was followed by related papers by Evans et al. [38, 48], focused in the initial phase on the reaction of mainly β,γ-unsaturated α-keto esters **53** with ethyl vinyl ether **46a** and 2,3-dihydrofuran **50a** (Scheme 4.34).

The enantioselective cycloaddition of the β,γ-unsaturated α-keto esters **53** with ethyl vinyl ether **46a** and 2,3-dihydrofuran **50a** catalyzed by **21b** (X=OTf) or the



Scheme 4.33



Scheme 4.34

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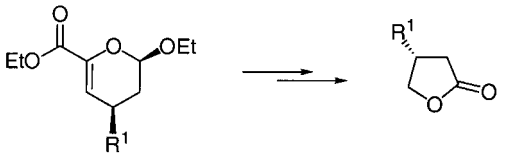
water complex **27** (Scheme 4.24) proceeds with high yield and diastereo- and enantioselectivity [38, 48, 49]. The reaction tolerates a broad range of R^1 substituents, such as alkyl, aryl, alkoxy, and thiobenzyl. The reaction can proceed with only 0.5 mol% catalyst **27b** with only a slight decrease in ee and diastereomeric excess [38b, 48b]. Preliminary studies have also indicated that catalyst **27b** can be re-used in multiple reaction cycles without significant loss in yield and stereoselectivity, and that the β,γ-unsaturated α-keto esters were somewhat more reactive than α,β-unsaturated acyl phosphonates in catalytic cycloaddition reactions.

The absolute configuration of the cycloaddition products **54a,b** was assigned by transformation to the lactones **66a,b** with known configuration (Scheme 4.35) [38b, 48b].



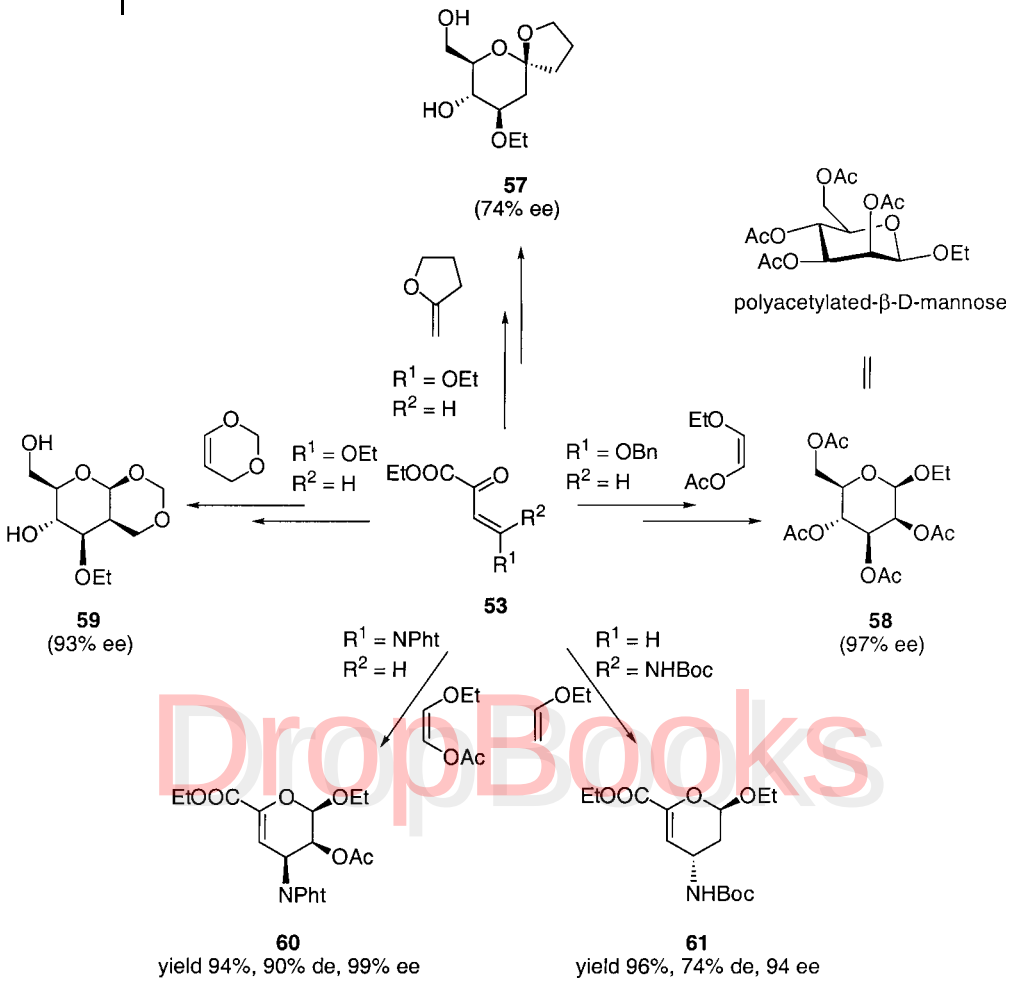
54 **56**

a: R^1 = Ph
b: R^1 = *i*-Pr

Scheme 4.35

Further developments of this inverse electron-demand catalytic enantioselective cycloaddition reaction using β-substituted β,γ-unsaturated α-keto esters **53** have resulted in simple approaches for the synthesis of optically active carbohydrates [39], including amino sugars [50], as outlined in Scheme 4.36. The reaction can be used for the preparation of optically active spiro carbohydrates **57**, an important functionality found in natural compounds such a pheromones, steroidal compounds, antiparasitic agents, and polyether antibiotics. *cis*-Alkenes are also useful substrates for inverse electron-demand catalytic enantioselective cycloaddition reaction of β,γ-unsaturated α-keto esters leading to the cycloaddition product in good yield and with very high de and ee. This reaction has been used for the synthesis of the ethyl β-D-manonose tetraacetate **58**. It is interesting to point out that the β-linkage at C-1 of the monosaccharides is difficult to synthesize by standard carbohydrate chemistry, because it is neither possible to use the neighboring-group effect at C-2, nor the anomeric effect. The cycloaddition approach can also be used as a synthetic procedure for the preparation of the non-naturally occurring acetal-protected C-2-branched carbohydrate **59**. The formation of amino sugars by this catalytic enantioselective reaction has shown that diastereomers **60** and **61**, with different protection groups, can be formed in high yield, de, and ee. Amino sugars can be applied as pharmaceuticals such as for the treatment of diabetes and are promising drugs against influenza.

The absolute configuration of products obtained in the highly stereoselective cycloaddition reactions with inverse electron-demand catalyzed by the *t*-Bu-BOX-Cu(II) complex can also be accounted for by a square-planar geometry at the copper(II) center. A square-planar intermediate is supported by the X-ray structure of the hydrolyzed enone bound to the chiral BOX-copper(II) catalyst, shown as **29b** in Scheme 4.24.



Scheme 4.36

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4.4 Summary

The major developments of catalytic enantioselective cycloaddition reactions of carbonyl compounds with conjugated dienes have been presented. A variety of chiral catalysts is available for the different types of carbonyl compound. For unactivated aldehydes chiral catalysts such as BINOL-aluminum(III), BINOL-titanium(IV), acyloxylborane(III), and tridentate Schiff base chromium(III) complexes can catalyze highly diastereo- and enantioselective cycloaddition reactions. The mechanism of these reactions can be a stepwise pathway via a Mukaiyama aldol intermediate or a concerted mechanism. For α-dicarbonyl compounds, which can coordinate to the chiral catalyst in a bidentate fashion, the chiral BOX-copper(II)

complexes have shown promising results. These complexes can catalyze cycloaddition reactions of glyoxylates, α-keto esters, α-diketones, and ketomalonate with conjugated dienes, leading to the cycloaddition product in high yield, diastereo- and enantioselectivity. Occasionally it was possible to perform the reactions with low catalyst loading. These normal electron-demand reactions proceed via different structural intermediates depending on the chiral ligand. The chiral BOX-copper(II) complexes can also be used as catalysts for inverse electron-demand cycloaddition reactions of α,β-unsaturated carbonyl compounds with electron-rich alkenes leading to a simple procedure for the formation 2-substituted 3,4-dihydro-2*H*-pyrans. These reactions also proceed in a highly selective manner and have been used for the synthesis of carbohydrates such as spiro carbohydrates, a β-D-manonose, and amino sugars.

Acknowledgment

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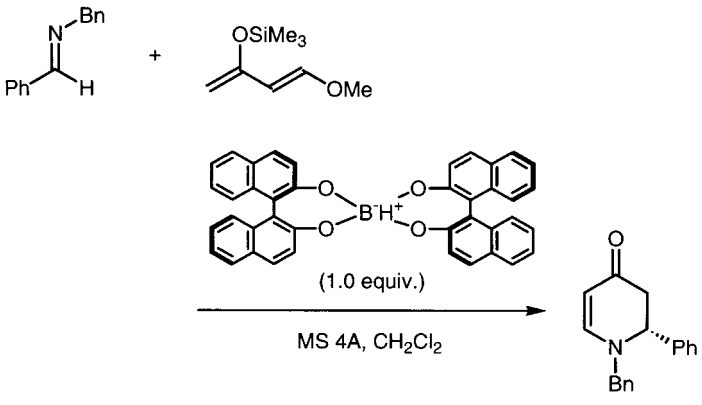
5
Catalytic Enantioselective Aza Diels-Alder Reactions

Shū Kobayashi

5.1
Introduction

Asymmetric aza Diels-Alder reactions provide a useful route to optically active nitrogen-containing heterocyclic compounds such as piperidines, tetrahydroquinolines, etc. [1]. Although successful examples of diastereoselective approaches using chiral auxiliaries have been reported [2], few examples of enantioselective reactions are known. This is in remarkable contrast to the recent progress achieved in asymmetric Diels-Alder reactions of carbon dienophiles or hetero-Diels-Alder reactions of carbonyl dienophiles with dienes. Although chiral Lewis acids have played leading roles in these reactions, it is assumed that most Lewis acids would be trapped by basic nitrogen atoms of the starting materials and/or products in aza Diels-Alder reactions, and that truly catalytic reactions would be difficult to perform. As a pioneering effort, Yamamoto et al. reported enantioselective aza Diels-Alder reactions of aldimines with Danishefsky's diene using chiral boron compounds (Scheme 5.1) [3]. Although high enantioselectivity was obtained, stoichiometric amounts of chiral sources were needed. This is also true in the above ex-



Scheme 5.1

78%, 86% ee

ample in which the chiral boron Lewis acids might be trapped by basic moieties of starting materials or products.

In 1996, the first example of the catalytic enantioselective aza Diels-Alder reactions of azadienes using a chiral lanthanide catalyst was reported [4]. In this article, successful examples of such catalytic reactions are surveyed.

5.2 Aza Diels-Alder Reactions of Azadienes

To achieve catalytic enantioselective aza Diels-Alder reactions, choice of metal is very important. It has been shown that lanthanide triflates are excellent catalysts for achiral aza Diels-Alder reactions [5]. Although stoichiometric amounts of Lewis acids are often required, a small amount of the triflate effectively catalyzes the reactions. On the basis of these findings chiral lanthanides were used in catalytic asymmetric aza Diels-Alder reactions. The chiral lanthanide Lewis acids were first developed to realize highly enantioselective Diels-Alder reactions of 2-oxazolidin-1-one with dienes [6].

The reaction of *N*-benzylideneaniline with cyclopentadiene was performed under the influence of 20 mol% of a chiral ytterbium Lewis acid prepared from ytterbium triflate ($Yb(OTf)_3$) [7], (*R*)-(+)-1,1′-binaphthol (BINOL), and trimethylpiperidine (TMP). The reaction proceeded smoothly at room temperature to afford the desired tetrahydroquinoline derivative in 53% yield, although no chiral induction was observed. At this stage, it was indicated that bidentate coordination between a substrate and a chiral Lewis acid would be necessary for reasonable chiral induction. Thus, *N*-benzylidene-2-hydroxyaniline (**1a**) was chosen as an imine, and the reaction with cyclopentadiene (**2a**) was examined. It was found that the reaction proceeded smoothly to afford the corresponding 8-hydroxyquinoline derivative (**3a**) in high yield. It is noted that some interesting biological activities were reported in 8-hydroxyquinoline derivatives [8]. Although the enantiomeric excess of the *cis* adduct in the first trial was only 6%, the selectivity increased when diazabicyclo-[5,4,0]-undec-7-ene (DBU) was used instead of TMP (Scheme 5.2, Table 5.1). It was also indicated that the phenolic hydrogen of **1a** would interact with DBU, which should interact with the hydrogen of (*R*)-(+)-BINOL [9], to reduce the selectivity. Several additives which interact with the phenolic hydrogen of **1a** were then examined. When 20 mol% of *N*-methylimidazole (NMI) was used, 91% ee of the *cis* adduct was obtained, but the chemical yield was low. When other additives were screened it was found that the desired tetrahydroquinoline derivative was obtained in 92% yield with high selectivity (*cis*/*trans*=>99/1, 71% ee), when 2,6-di-*t*-butyl-4-methylpyridine (DTBMP, **4a**) was used [4].

Other substrates were tested; the results are summarized in Table 5.2. Vinyl ethers (**2b**–**2d**) also worked well to afford the corresponding tetrahydroquinoline derivatives (**3a**–**3e**) in good to high yields with good to excellent diastereo- and enantioselectivity (entries 1–10). Use of 10 mol% of the chiral catalyst also gave the adducts in high yields and selectivity (entries 2 and 6). As for additives, 2,6-di-*t*-bu-

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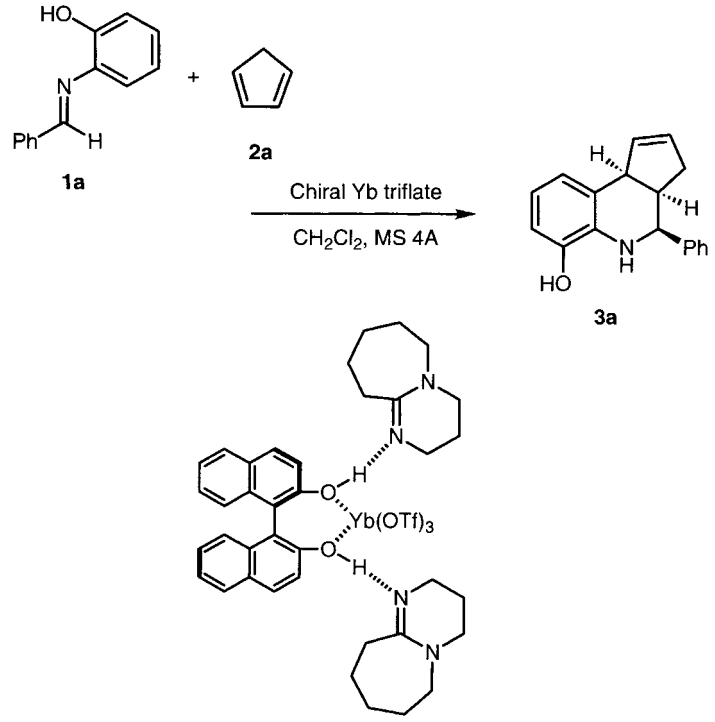
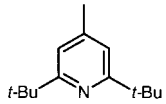


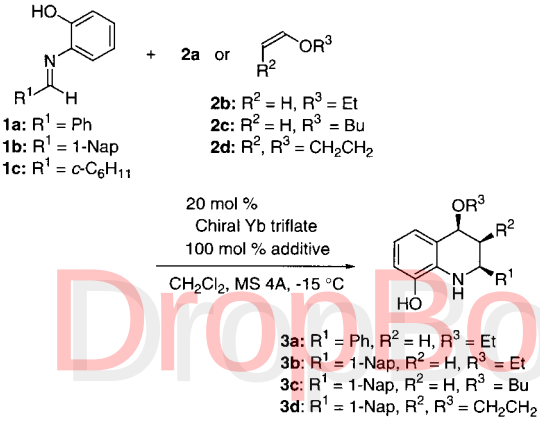
Scheme 5.2 Catalytic enantioselective aza Diels-Alder reaction (1)

Tab. 5.1 Effect of additives in the asymmetric aza Diels-Alder reaction

Entry	*Additive*	*Temp. (°C)*	*Yield (%)*	*cis/trans*	*ee (%) (cis)*
1	–	0	71	98:2	62
2	–	–15 to 0	48	99:1	68
3	(20 mol%)	–15 to 0	21	98:2	91
4	 **4a** (100 mol%)	–15	92	>99:1	71

tylpyridine (DTBP, **4b**) gave the best result in the reaction of imine **1a** with ethyl vinyl ether (**2b**), whereas higher selectivity was obtained when DTBMP (**4a**) or 2,6-diphenylpyridine (DPP, **4c**) was used in the reaction of imine **1b** with **2b**. This could be explained by the slight difference in the asymmetric environment created by $Yb(OTf)_3$, (*R*)-(+)-BINOL, DBU, and the additive. While use of butyl vinyl ether (**2c**) reduced selectivity (entry 7), dihydrofuran (**2d**) reacted smoothly to achieve high selectivity (entries 8 and 9). It was found that the imine (**1c**) prepared from cyclohexanecarboxaldehyde and 2-hydroxyaniline was unstable and difficult to purify. The asymmetric aza Diels-Alder reaction was successfully per-

Tab. 5.2 Catalytic enantioselective aza Diels-Alder reactions using azadienes



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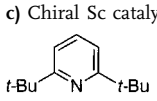
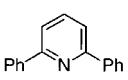
Entry	*Imine*	*Alkene*	*Product*	*Additive*	*Yield (%)*	*cis/trans*	*ee (%) (cis)*
1 a)	**1a**	**2b**	**3a**	**4b**	58	94:6	61
2 a, b)	**1a**	**2b**	**3a**	**4b**	52	94:6	77
3	**1b**	**2b**	**3b**	**4b**	69	>99:<1	86
4	**1b**	**2b**	**3b**	**4c**	65	99:1	91
5	**1b**	**2b**	**3b**	**4a**	74	>99:<1	91
6 b)	**1b**	**2b**	**3b**	**4a**	62	98:2	82
7	**1b**	**2c**	**3c**	**4a**	80	66:34	70
8	**1b**	**2d**	**3d**	**4a**	90	91:9	78
9	**1b**	**2d**	**3d**	**4c**	67	93:7	86
10 c)	**1c**	**2a**	**3e**	**4a**	58	>99:<1	73

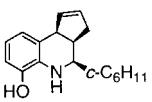
a) The reaction was performed at –45 °C
b) 10 mol% of the chiral Yb triflate was used
c) Chiral Sc catalyst was used



4b



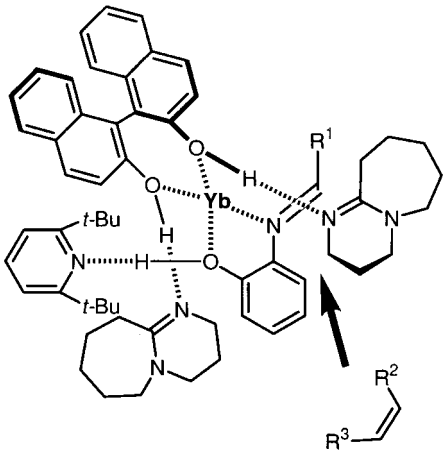
4c



3e

formed using the three-component-coupling procedure (successively addition of the aldehyde, the amine, and cyclopentadiene) in the presence of Sc(OTf) [6d, 7a, 10] (instead of $Yb(OTf)_3$), (*R*)-(+)-BINOL, DBU, and DTBMP (**4a**).

The assumed transition state of this reaction is shown in Scheme 5.3. $Yb(OTf)_3$, (*R*)-(+)-BINOL, and DBU form a complex with two hydrogen bonds, and the axial chirality of (*R*)-(+)-BINOL is transferred via the hydrogen bonds to the amine parts. The additive would interact with the phenolic hydrogen of the imine, which is fixed by bidentate coordination to Yb(III). Because the top face of the imine is shielded by the amine, the dienophiles approach from the bottom face to achieve high levels of selectivity.



Scheme 5.3 Assumed transition state (triflate ions are omitted for clarity)

(i) Asymmetric aza Diels-Alder reactions between achiral azadienes and dienophiles have been achieved using a catalytic amount of a chiral source.
(ii) The unique reaction pathway in which the chiral Lewis acid activates not dienophiles but dienes, has been revealed. In most asymmetric Diels-Alder reactions reported using chiral Lewis acids, the Lewis acids activate dienophiles [11].
(iii) A unique lanthanide complex including an azadiene and an additive, which is quite different from the conventional chiral Lewis acids, has been developed.

5.3 Aza Diels-Alder Reactions of Azadienophiles

While the above results have demonstrated the catalytic enantioselective aza Diels-Alder reactions of azadienes, the catalytic enantioselective aza Diels-Alder reactions of azadienophiles were reported using a chiral zirconium compound.

Chiral zirconium compound **6** [12] was prepared from $Zr(Ot\text{-}Bu)_4$, 2 equiv. (*R*)-6,6′-Br-1,1′-binaphthol ((*R*)-Br-BINOL, **5**) [13], and 2–3 equiv. of a ligand

(Scheme 5.4), and the model reaction of the imine derived from 1-naphthaldehyde and 2-aminophenol (**1b**) with Danishefsky's diene (**7a**) [14] was investigated. It was found that ligands and solvents strongly influenced the yields and enantioselectivity (Table 5.3). The importance to the selectivity of the free hydroxyl group of the aldimine was already known [4, 12]. Actually, when the imine prepared from aniline or 2-methoxyaniline was used under the same reaction conditions, the corresponding pyridone derivatives were obtained in good yields but low ee (aniline, 68% yield, 4% ee; 2-methoxyaniline, 74% yield, 25% ee). For ligands, *N*-methylimidazole (NMI) gave the best result. When the chiral catalyst (10 mol%) was prepared in dichloromethane, the desired aza Diels-Alder reaction of aldimine **1b** with diene (**7a**) proceeded smoothly, but the enantiomeric excess of the adduct was only 40%. On the other hand, the enantioselectivity was improved to 61% ee when the catalyst was prepared in benzene by stirring at room temperature for 1 h, the mixture was evaporated to remove benzene and *t*-BuOH under reduced pressure, and the reaction was then performed in dichloromethane. Although use of a bulky diene (4-*t*-butoxy-2-trimethylsiloxy-1,3-butadiene, **7b**) [15] reduced the selectivity in this instance, a higher enantiomeric excess was obtained when the catalyst was prepared in toluene. The best result was finally obtained when the preparation of the catalyst and the successive reaction was carried out in toluene (without removing the solvent) [16].

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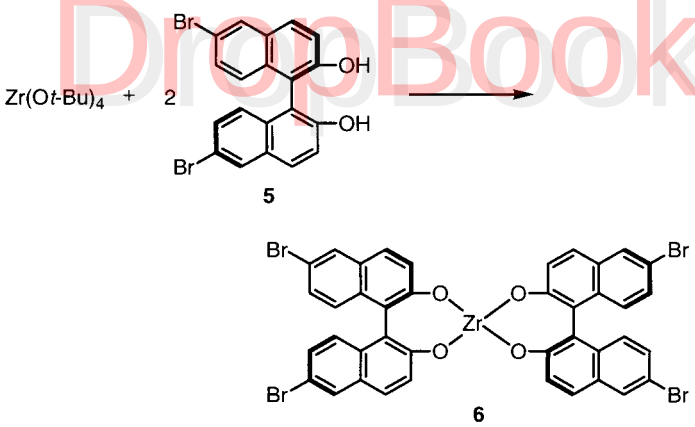
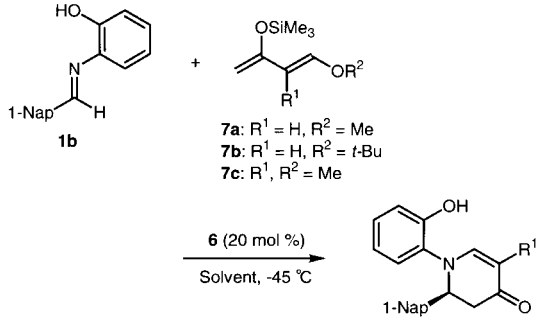


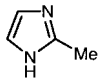
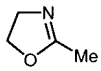
Scheme 5.4 Preparation of chiral zirconium catalyst (**6**)

The effect of the metals used was then examined (Table 5.4). When the group 4 metals, titanium, zirconium, and hafnium, were screened it was found that a chiral hafnium catalyst gave high yields and enantioselectivity in the model reaction of aldimine **1b** with **7a**, while lower yields and enantiomeric excesses were obtained using a chiral titanium catalyst [17].

Several examples of catalytic aza Diels-Alder reactions using the chiral zirconium catalyst are shown in Table 5.5 [18]. High chemical yields and good to high

Tab. 5.3 Catalytic enantioselective aza Diels-Alder reactions using imino dienophiles (1)

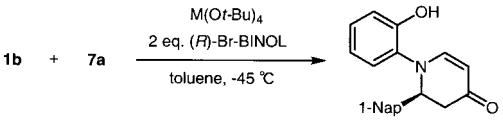


Entry	*Additive (mol%)*	*Solvent*	*Yield (%)*	*ee (%)*
1	NMI (30)	CH_2Cl_2	74	40
2	NMI (30)	C_6H_6↑–CH_2Cl_2	81	61
			(83	41) a)
3	NMI (30)	Toluene↑–CH_2Cl_2	81	71
4	NMI (30)	Toluene	86	82
5	DMI (20)	Toluene	76	59
6	 (30)	Toluene	28	24
7	(30)	Toluene	86	50
8	 (30)	Toluene	81	46
9	–	Toluene	65	10 b)

a) 4-*t*-Butoxy-2-trimethylsilyloxy-1,3-butadiene (**7b**) was used
b) Reverse enantioselectivity was observed

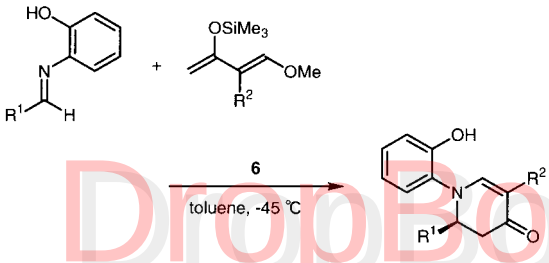
enantioselectivity was usually obtained in the presence of 5–20 mol% of the chiral catalyst. 4-Methoxyl-3-methyl-2-trimethylsiloxy-1,3-butadiene (**7c**) [19] also worked well under standard conditions and the desired 2,3-dihydro-4-pyridone derivatives were obtained in high yields with high enantioselectivity. As for the R^1 group in Table 5.5, *ortho*-substituted aromatic compounds gave higher selectivity. For example, although the imine derived from benzaldehyde (**1a**) reacted with **7c** to afford the corresponding adduct in 65% ee (Table 5.5, entry 10), 77% ee of the pyridone derivative was obtained in the reaction of the imine derived from *o*-tolualdehyde (**1d**) with **7c** under the same reaction conditions (entry 9). The imine derived

Tab. 5.4 Effect of metals



Entry	*M (catalyst)*	*mol%*	*Yield (%)*	*ee (%)*
1	Zr (**6**)	10	86	82
2	Zr (**6**)	20	96	88
3	Hf	10	89	73
4	Hf	20	96	84
5	Ti	10	68	39
6	Ti	20	70	62

Tab. 5.5 Catalytic enantioselective aza Diels-Alder reactions using imino dienophiles (2)



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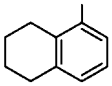
Entry	*R¹*	*Diene*	*Amount of 5 (mmol)*	*Yield (%)*	*ee (%)*
1	1-Nap (**1b**)	**7a**	5	72	67
2			10	86	82
3			20	96	88
4		**7c**	10	79	89
5			20	93	93
6		**7a**	10	92	80
7	*o*-Me-Ph (**1d**)	**7a**	10	81	76
8			20	83	82
9		**7c**	20	97	77
10	Ph (**1a**)	**7c**	20	83	65
11		**7a**	10	86	64
12	*c*-C_6H_{11} (**1c**)	**7c**	10	47	78 a)
13			20	51	86 a)

a) The imine was prepared from cyclohexanecarboxaldehyde and 2-amino-3-methylphenol

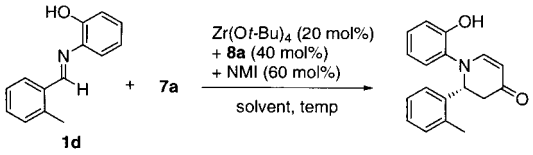
from 2-thiophenecarboxyaldehyde reacted with **7a** smoothly to give the corresponding pyridone derivative in high yield and good enantiomeric excess. In the reaction of the imine derived from cyclohexanecarboxaldehyde (**1c**) with **7c**, low enantiomeric excess of the adduct was observed under standard reaction conditions. The low selectivity was attributed to isomerization of the *cis* and *trans* conformation of the aldimine. To prevent the isomerization, the imine derived from cyclohexanecarboxaldehyde and 2-amino-3-methylphenol was used. As expected, the enantiomeric excess of the corresponding pyridone derivative was improved to 86% ee.

5.4 A Switch of Enantiofacial Selectivity

Synthesis of both enantiomers is a very important task not only in organic chemistry but also in medicinal and bioorganic chemistry [20]. In chemical transformations, syntheses of both enantiomers are generally performed using both enantiomers of chiral sources. Although there are many chiral sources in nature, it is sometimes difficult to obtain both enantiomers, for example those of amino acids, monosaccharides, alkaloids, etc. When such chiral sources are employed in asymmetric syntheses, preparation of both enantiomers is difficult. Mechanistically, on the other hand, both enantiomers can be produced by controlling the enantiofaces of prochiral compounds. It should, therefore, be possible to control them by designing ligands which even have the same chirality [21, 22].

On the basis of this consideration the catalyst-substrate interaction, including the reaction course in chiral zirconium-catalyzed aza Diels-Alder reactions, was examined. It was indicated from both experiments and modeling studies that the substituents at the 3,3′-positions of the BINOL ligand strongly influenced enantioselectivity [23]. In the presence of $Zr(O\textit{t}\text{-}Bu)_4$ (20 mol%), (*R*)-6,6′-dibromo-3,3′-diphenyl-1,1′-binaphthol (**8a**, 40 mol%), and NMI (60 mol%), imine **1d**, prepared from *o*-tolualdehyde and 2-aminophenol, reacted with Danishefsky's diene (**7a**) in toluene at –45 °C to afford the corresponding piperidine derivative in 84% ee (Table 5.6, entry 1). The absolute configuration was proved to be (*R*), which was the reverse of that using (*R*)-Br-BINOL (**5**) instead of **8a** under the same reaction conditions (entry 2). Several reaction conditions were examined and interesting effects of molecular sieves (MS) were found. When the reaction was conducted at 0 °C without molecular sieves the enantioselectivity decreased to 57% ee (entry 3). In contrast, 90% ee of the product was obtained when MS 3 Å was added to the reaction pot (entry 4). Although MS 4 Å and 5 Å were also effective, the enantioselectivity decreased when the reaction was performed at –45 °C with MS 3 Å (entries 5–7). Furthermore, the best result was obtained when the reaction was performed at 23 °C in benzene (entries 8 and 9). It is noted that the chemical yield was also improved by more than 25% and that 91% ee of the product was obtained even at 23 °C. When 10 mol% of the catalyst was used, chemical yield and enantioselectivity decreased (81%, 77% ee).

Tab. 5.6 Effect of solvents, temperature, and molecular sieves



Entry	*Solvent*	*Temp. (°C)*	*MS*	*Yield (%)*	*ee (%)*
1	Toluene	–45	None	66	84
2	Toluene	–45	None	83	82 (*S*) a)
3	Toluene	0	None	45	57
4	Toluene	0	MS 3 Å	80	90
5	Toluene	0	MS 4 Å	76	89
6	Toluene	0	MS 5 Å	77	89
7	Toluene	–45	MS 3 Å	54	77
8	Toluene	23	MS 3 Å	96	88
9	Benzene	23	MS 3 Å	93	91

a) Catalyst **6** was used

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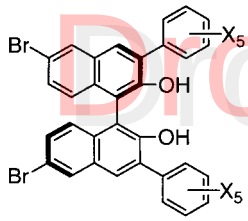
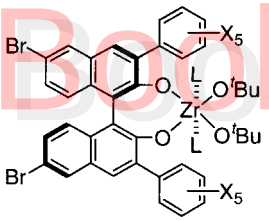
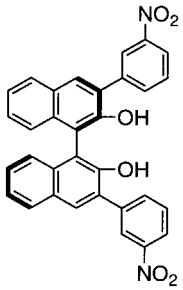


8a: X = H
8b: X = D



L = NMI

9a: X = H
9b: X = D

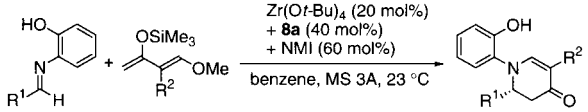


10

Chart 5.1

Other examples were tested and the results are summarized in Table 5.7 [24]. The reactions always proceeded smoothly to afford the corresponding piperidine derivatives in high yields with high enantiomeric excess. In addition, reverse enantio-

Tab. 5.7 Catalytic asymmetric aza Diels-Alder reactions



Entry	R^1	R^2	*Yield (%)*	*ee (%)*
1	Ph (**1a**)	H	94	82
2	Ph (**1a**)	Me	Quant.	80
3	*o*-MePh (**1d**)	H	93	91
4	*o*-MePh (**1d**)	Me	98	89
5	*α*-Nap (**1b**)	H	88	84
6	*α*-Nap (**1b**)	Me	78	80
7		H	67	85
8		Me	78	87
9		H	90	90
10		Me	87	88
11	2-thiophene	H	74	86 a)
12	2-thiophene	Me	70	86 a)
13	*c*-C_6H_{11} (**1c**)	H	64	81 b)
14	*c*-C_6H_{11} (**1c**)	Me	67	80 b)

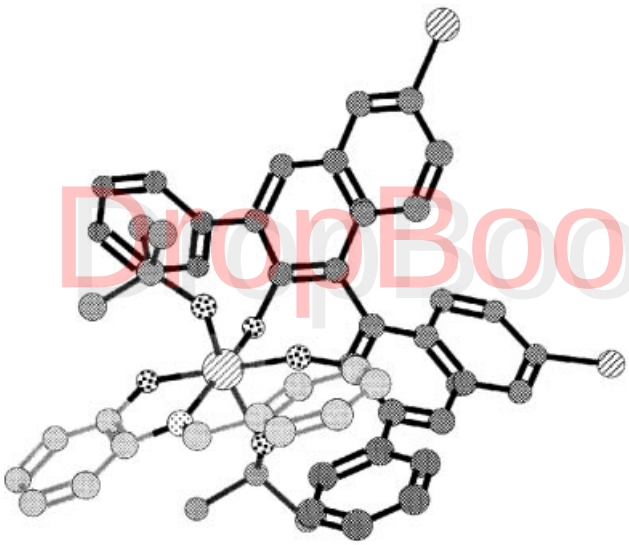
a) 10 was used instead of **8a**
b) The imine was prepared from cyclohexanecarboxaldehyde and 2-amino-3-methylphenol

selectivity was observed in these reactions compared with those obtained using **6** as a catalyst. It is noteworthy that chemical yields and enantiomeric excesses were usually improved by using the new catalyst system.

The precise structure of the zirconium catalyst was examined by NMR analysis. When Zr(O*t*-Bu)$_4$ (1 equiv.), **8b** (2 equiv.), and NMI (3 equiv.) were combined in benzene-d_6 at 23 °C, two independent species which were assigned to a new zirconium catalyst and free **8b** were observed. Although the signals of free **8b** were still observed when Zr(O*t*-Bu)$_4$ (1 equiv.), **8b** (1 equiv.), and NMI (3 equiv.) were stirred at 23 °C, only the signals assigned to the new zirconium catalyst were detected when the mixture was stirred at 80 °C for 2.5 h. These results indicated the formation of **9b** as the new zirconium catalyst. The structure was also supported by an experiment in which Zr(O*t*-Bu)$_4$ (0.2 equiv.), **8a** (0.2 equiv.), NMI (0.6 equiv.), and MS 3 Å were combined in benzene and the mixture was stirred for 2.5 h at 80 °C (formation of **9a**). Imine **1d** (1 equiv.) and **7a** (1.2 equiv.) were then added to the catalyst solution, and the mixture was stirred for 48 h at 23 °C. After the same work-up procedures as described above, the desired piperidine derivative was obtained in >98% yield with 89% ee, values comparable with those

obtained when the catalyst was prepared by combining $Zr(Ot\text{-}Bu)_4$ (1 equiv.), **8a** (2 equiv.), and NMI (3 equiv.) at 23 °C (Table 5.7, entry 3). It was assumed that formation of **9** was slow and incomplete at 23 °C, because of the bulky 3,3′-phenyl groups of **8**.

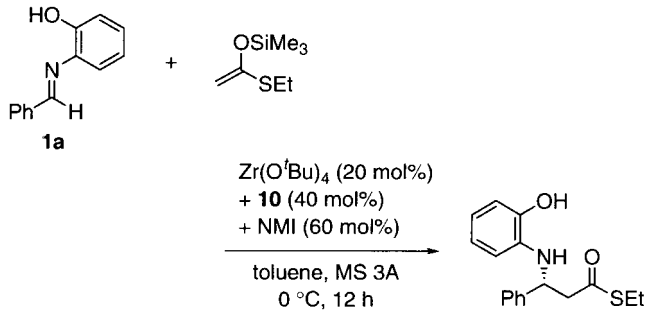
The assumed transition state for this reaction is shown in Scheme 5.5. The two bulky *t*-butoxy groups are expected to locate at the two apical positions. One of the 3,3′-phenyl groups would effectively shield one face of an imine, and consequently, a diene attacks from the opposite side. Judging from this model, similar selectivities were expected in the Mannich-type reactions of imines with silyl enolates. Actually, when ligand **10** was used in the reaction of imine **1a** with *S*-ethylthio-1-trimethylsiloxyethene, the corresponding *β*-amino thioester was obtained in 84% ee (Scheme 5.6). As expected, the sense of the chiral induction in this case was the reverse of that observed when using catalyst **6** [12, 25].



Scheme 5.5 Assumed transition state

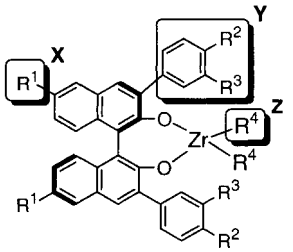
5.5 Chiral Catalyst Optimization

Although high yields and selectivity were sometimes attained in chiral zirconium-catalyzed aza Diels-Alder reactions, further optimization of the catalyst structure was desired. In addition, another problem was the rather high loading of the catalyst (10–20 mol%). To address these issues, optimization of the catalyst structure was planned using both solid-phase and liquid-phase methods. Solid-phase and liquid-phase methods have advantages and disadvantages, and it is believed that combining the advantages of these methods leads to the most efficient catalyst optimization.



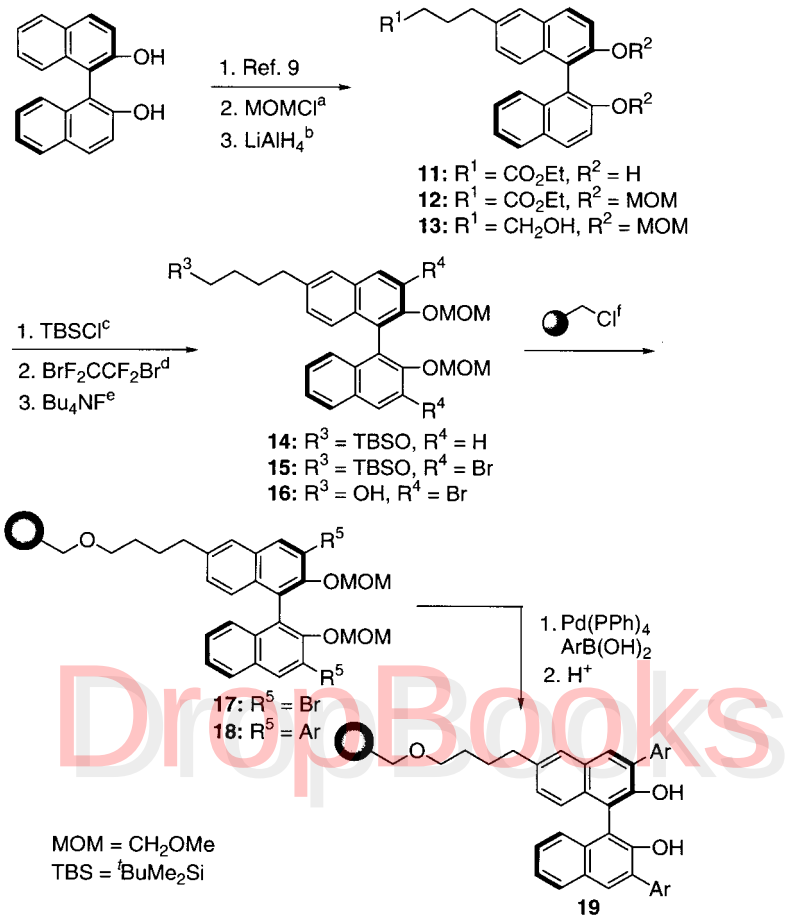
Scheme 5.6 Mannich-type reaction

The catalyst was divided into three parts (X, Y, Z in Scheme 5.7). First, to optimize Y, polymer-supported (*R*)-1,1′-binaphthol (BINOL) derivatives were prepared [26]. The synthetic route is shown in Scheme 5.8. 6-Tethered (*R*)-BINOL derivative **11** was readily prepared from BINOL [27]. After MOM protection (**12**), the ester moiety of **12** was reduced with lithium aluminum hydride ($LiAlH_4$) to give **13**, the hydroxyl group of which was protected as its *tert*-butyldimethylsilyl (TBS) ether (**14**). The 3,3′-positions of **14** were then brominated via an aromatic lithium intermediate to afford **15** and, after deprotection of the TBS ether (**16**), 1% divinylbenzene-cross-linked polystyrene (Merrifield resin) was used as a polymer support to form **17**. A key step to introduce aryl substituents at the 3,3′-positions of **17** was performed using the Suzuki reaction with boronic acids under the influence of a palladium catalyst [28]. After deprotection of the MOM groups of **18** the desired polymer-supported BINOL derivatives (**19**) were obtained successfully. All the solid-phase reactions were monitored by ^{1}H and ^{13}C swollen-resin magic angle spinning (SR MAS) NMR [29].



Scheme 5.7

Polymer-supported BINOLs thus prepared were treated with $Zr(Ot\text{-}Bu)_4$ to form polymer-supported zirconium **20**. In the presence of 20 mol% of various zirconium **20**, the model aza Diels-Alder reactions of imine **1d** with Danishefsky's diene (**7a**) were performed; results from selected examples are shown in Table 5.8. Whereas the 4-*t*-butylphenyl group resulted in lower enantiomeric excess (ee), higher ee were obtained when 3,5-xylyl, 4-biphenyl, 4-fluorophenyl, and 3-tri-

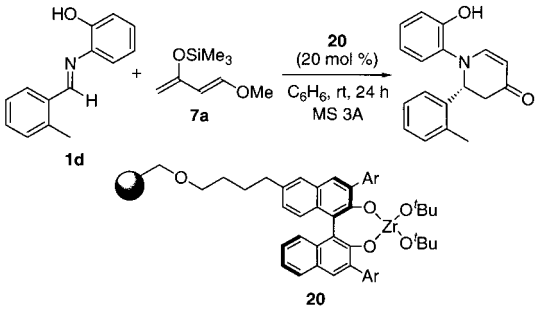


[a](a) MOMCl, NaH, DMF, rt, 95%; (b) $LiAlH_4$, THF/Et_2O, rt, quant; (c) TBSCl, imidazole, DMF, rt, 98%; (d) 1. BuLi; 2. BrF_2CCF_2Br, 90%; (e) Bu_4NF, THF, rt, 95%; (f) Merrifield resin, NaH, Bu_4NI, 81%.

Scheme 5.8 Synthesis of polymer-supported BINOLs

fluoromethylphenyl groups were introduced at the 3,3′-positions of the BINOLs. Among these the 4-fluorophenyl and 3-trifluoromethylphenyl groups were the most promising in both yield and selectivity. One advantage using polymer-supported BINOLs is that the ligand can be easily recovered by simple filtration and re-used. For example, in the reaction of **1d** with 1-methoxy-2-methyl-3-trimethylsiloxy-1,3-butadiene (**7c**) in the presence of 20 mol% **20a** (Ar = 3-trifluoromethylphenyl); 1st run, >99% yield, 91% ee; 2nd run, 97% yield, 90% ee; 3rd run, 97% yield, 90% ee. It is also noted that many chiral ligands were synthesized and optimized rapidly using the solid-phase methods.

Tab. 5.8 Catalyst optimization using **20** in the reaction of **1d** with **7a**



Ar	*Yield (%)*	*ee (%)*
Phenyl	61	77
m-Tolyl	80	73
o-Tolyl	80	72
4-*tert*-Butylphenyl	58	48
3,5-Xylyl	70	82
4-Biphenyl	59	80
2-Naphthyl	74	74
6-Methoxy-2-naphthyl	61	70
4-Fluorophenyl	80 (78) a)	83 (88) a)
3,4-Difluorophenyl	82	71
3-Trifluoromethylphenyl (**20a**)	87 (>99) a)	80 (91) a)
3,5-bis(Trifluoromethyl)phenyl	92	60
3-Methoxyphenyl	75	76
4-Methoxyphenyl	75	41
3,4-Dimethoxyphenyl	82	60
4-Ethoxyphenyl	63	59
2-Thienyl	61	44

a) 1-Methoxy-2-methyl-3-trimethysiloxy-1,3-butadiene (**7c**) was used instead of **7a**

Next, the X and Z parts were optimized using liquid-phase methods. Several zirconium catalysts were prepared and were tested in the model reaction of **1d** with **7a**. The results are summarized in Table 5.9. Higher selectivity was obtained when electron-withdrawing cyano groups were introduced at the R^4 positions. Higher selectivity was also observed when electron-withdrawing groups such as fluoro and trifluoromethyl groups were employed at the R^2 and R^3 positions. It was, in addition, revealed that slow addition of the substrates to the catalyst was effective. Finally, 94% ee of the aza Diels-Alder adduct was obtained when only 2 mol% of the catalyst (**20f**) was employed.

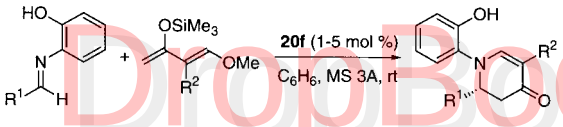
Several examples of catalytic asymmetric aza Diels-Alder reactions are shown in Table 5.10 [30]. The reaction always proceeded smoothly to afford the correspond-

Tab. 5.9 Catalyst optimization using **10** in the reaction of **1d** with **7a**

R^1	R^2	R^3	R^4	Amount catalyst (mol%)	Yield (%)	ee (%)
H	H	H	*t*-BuO (**20a**)	20	92	77
Br	H	H	*t*-BuO (**20b**)	20	93	91
Br	H	H	*t*-BuO (**20b**)	10	81	77
Br	H	H	*t*-BuO (**20b**)	5	75	52
Br	H	H	CN (**20c**)	20	94	94
Br	H	H	CN (**20c**)	10	90	88
Br	H	H	CN (**20c**)	5	84 (92) a)	68 (92) a)
Br	H	H	CN (**20c**)	2	77 (83) a)	47 (80) a)
H	F	H	CN (**20d**)	2	59	73
Br	F	H	CN (**20e**)	2	70 (70) a)	77 (85) a)
H	H	CF_3	CN (**20f**)	2	73 (68) a)	87 (94) a)
Br	H	CF_3	CN (**20g**)	2	74	88

a) A mixture of **1d** and **7a** was added to the catalyst over a period of 1 h

Tab. 5.10 Catalytic asymmetric aza Diels-Alder reactions



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R^1	R^2	Amount catalyst (mol %)	Yield (%)	ee (%)
Ph	H	5	76	92
Ph	Me	5	81	91
o-MePh	H	5	93	91
o-MePh	H	2	68	94
o-MePh	H	1	64	83
o-MePh	Me	2	72	88
α-Nap	H	5	80	92
α-Nap	H	2	67	86
α-Nap	Me	2	71	84
	H	5	75	90
	Me	2	68	90
2-Thiophene	H	2	61	83
c-C_6H_{11}	Me	5	75	84 a)

a) The imine was prepared from cyclohexanecarboxaldehyde and 2-amino-3-methylphenol

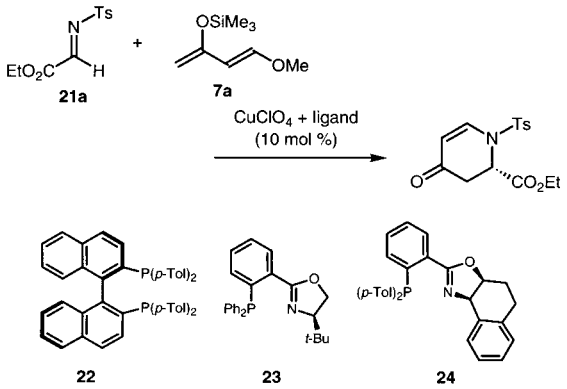
ing piperidine derivatives in good to high yields and high enantiomeric excess using 1–5 mol% of the chiral zirconium catalyst.

Thus, a novel chiral zirconium complex for asymmetric aza Diels-Alder reactions has been developed by efficient catalyst optimization using both solid-phase and liquid-phase approaches. High yields, high selectivity, and low loading of the catalyst have been achieved, and the effectiveness of chiral catalyst optimization using a combination of solid-phase and liquid-phase methods has been demonstrated.

5.6
Aza Diels-Alder Reactions of α-Imino Esters with Dienes

α-Imino esters (**21a**) are reactive electrophiles and dienophiles. It has been found that *N*-tosyl-α-imino ester reacted with Danishefsky's diene (**7a**) in the presence of a catalytic amount of a chiral Lewis acid to afford the corresponding aza Diels-Alder adduct in a highly stereoselective manner [31]. Several combinations of Lewis acids and chiral ligands were screened, and it was revealed that $CuClO_4$ combined with Tol-BINAP (**22**) and phosphinooxazoline ligands (**23** and **24**) gave the highest enantioselectivity (Table 5.11). Although CuOTf and $CuPF_6$ were available, other Lewis acids such as $Zn(OTf)_4$, $Cu(OTf)_2$, $AbSbF_6$, AgOTf, $AgClO_4$, $Pd(SbF_6)_2$, $Pd(ClO_4)_2$, $Pd(OTf)_2$, and $RuSbF_6$ resulted in significantly lower enantiomeric excess, even though good yields of the desire adducts were obtained by using these Lewis acids.

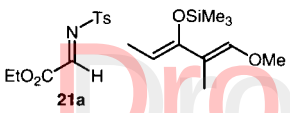
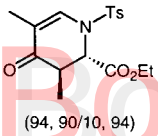
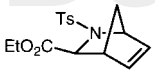
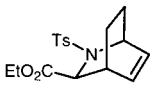
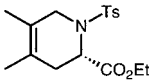
Tab. 5.11 Aza Diels-Alder reaction of α-imino esters



Ligand	*Solvent*	*Yield (%)*	*ee (%)*
22	THF	80	79
23	THF	82	87
24	CH_2Cl_2	77	86

Several other dienes were then tested in chiral Cu-catalyzed aza Diels-Alder reactions (Table 5.12). When *trans*-1-methoxy-2-methyl-3-(trimethylsiloxy)-1,3-pentadiene was treated with *α*-imino ester **21a** in the presence of 10 mol% $CuClO_4$-Tol-BINAP, the desired adduct was obtained in high yield with high diastereo- and enantioselectivity (91% yield, *trans*/*cis*=90/10, 94% ee (*trans*)). The reaction also proceeded smoothly even in the presence of 1 mol% of the catalyst (76% yield, *trans*/*cis*=92/8, 96% ee (*trans*)). It was noted that the *exo-trans* adduct was obtained preferentially. The reaction would proceeded via the *E* isomer of imine **21a** and *N*-tosyl substituent adapting an *endo* orientation relative to the diene in the transition state to afford the *exo* adduct (Scheme 5.9). In addition, non-activated dienes such as cyclopentadiene, cyclohexadiene, and isoprene also reacted with *α*-imino ester **21a** to afford the aza Diels-Alder adducts in good to high yields with good enantiomeric excess. Although these dienes are known to be less reactive than Danishefsky's diene (**7a**), they reacted smoothly in these chiral Cu-catalyzed reactions.

Tab. 5.12 Aza Diels-Alder reactions using several dienes

Dienophile	*Diene*	*Solvent*	*Major product (Yield, exo/endo, ee)*
 **21a**		THF	 (94, 90/10, 94)
		CH_2Cl_2	 (93, 92/8, 83)
		CH_2Cl_2	 (59, 92/8, 83)
		THF	 (64, 65)

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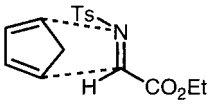
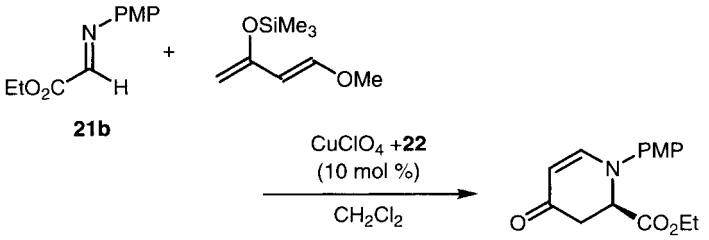
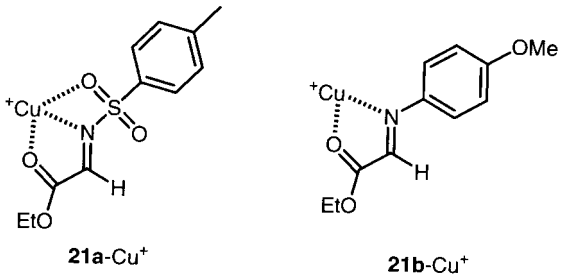
For imines, *α*-imino esters with an *N*-*p*-methoxyphenyl substituent (**21b**) also reacted with Danishefsky's diene in the presence of 10 mol% of $CuClO_4$-Tol-BINAP to give the corresponding adduct in high yield with good enantiomeric excess (Scheme 5.10). Remarkably, reverse enantioselectivity was observed when the *α*-imino esters **21a** and **21b** were used. This notable selectivity was explained by as-



Scheme 5.9 Assumed transition state



Scheme 5.10



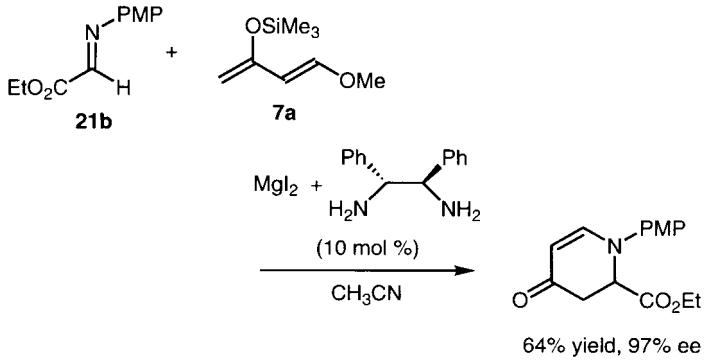
Scheme 5.11 Assumed coordination forms

suming tridentate and bidentate coordination, respectively, of the imines to copper (I), as shown in Scheme 5.11. The solvents, THF and CH_2Cl_2, might also affect the transition states and the selectivity.

A chiral magnesium catalyst prepared from magnesium iodide and 1,2-diphenylethylenediamine was also found to be effective in asymmetric aza Diels-Alder reaction of α-imino ester **21b** with **7a** (Scheme 5.12) [32]. The novel catalyst was discovered using parallel combinatorial methods.

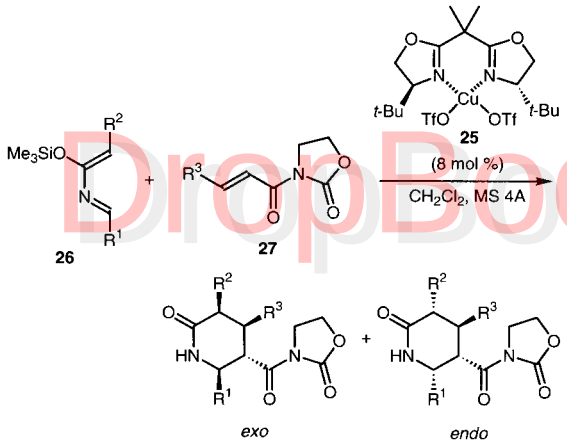
5.7
Aza Diels-Alder Reactions of 2-Azadienes

In the presence of 10 mol% chiral Cu(II) catalyst **25**, 2-azadienes **26** reacted with dienophiles **27** to afford the corresponding piperidone derivatives in high yields



Scheme 5.12

Tab. 5.13 Catalytic asymmetric aza Diels-Alder reactions of 2-azadienes



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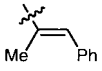
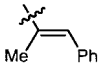
R^1	R^2	R^3	Temp. (°C)	Yield (%)	exo/endo	ee (%) (exo)
Ph	Me	Me	–45	80	>99:1	95
Ph	Me	Me	Room temp.	96	>99:1	94
Ph	H	H	–45	83	86:14	98
Ph	Me	H	–45	96	>99:1	98
Ph	H	Me	Room temp.	80	>99:1	93
	Me	Me	Room temp.	98	>99:1	90
	Me	Me	–45	62	>99:1	95

and high enantiomeric excess (Table 5.13) [33]. This reaction provides a useful route for the synthesis of optically active piperidine derivatives.

5.8 Perspective

Several examples of catalytic asymmetric aza Diels-Alder reactions have been surveyed. In the presence of catalytic amounts of chiral Lewis acids based on Yb, Zr, Cu, and Mg high yields and high diastereo- and enantioselectivity have been achieved. Important to these successes was the choice of the metals of the chiral Lewis acids. These reactions will be used for the synthesis of biologically important nitrogen-containing compounds. On the other hand, activated dienophiles and/or activated dienes often have to be used in these reactions, and turnover numbers of the catalysis are not always sufficient. These problems will be addressed by designing more efficient chiral Lewis acids. Catalytic asymmetric intramolecular aza Diels-Alder reactions, which have not yet been achieved, would, moreover, provide a useful route to optically active complexed nitrogen-containing cyclic compounds.

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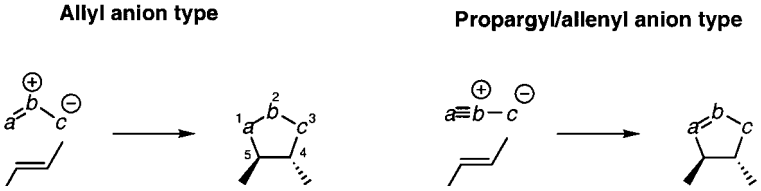
6
Asymmetric Metal-catalyzed 1,3-Dipolar Cycloaddition Reactions

Kurt Vesterager Gothelf

6.1
Introduction

The 1,3-dipolar cycloaddition reaction is the single most important method for the construction of heterocyclic five-membered rings in organic chemistry [1, 2]. Concerted cycloaddition reactions are also among the most powerful tools for the stereospecific creation of new chiral centers in organic molecules. When 1,2-disubstituted alkenes are involved in concerted 1,3-dipolar cycloaddition reactions, two new chiral centers on the alkene are formed in a stereospecific manner because of the *syn* attack on the double bond. This is shown for reactions of allyl anion-type and propargyl/allenyl anion-type 1,3-dipoles in Scheme 6.1. Thus, the relative stereochemistry at C-4 and C-5 is always controlled by the geometric relationship of the substituents on the alkene for concerted 1,3-dipolar cycloaddition reactions [3, 4]. Depending on the structure of the dipole, up to four new contiguous chiral centers can be formed in the 1,3-dipolar cycloaddition reaction in a single step and the current challenge for 1,3-dipolar cycloaddition reactions is to control the absolute stereoselectivity of the reaction by the application of chiral metal catalysts.



Scheme 6.1

Asymmetric synthesis is a stimulating academic challenge, but since it has become clear that most chiral drugs can be administered safely only in the enantiomerically pure form, the industrial need for asymmetric methods has made research in asymmetric synthesis absolutely necessary [5]. This has driven a renaissance in the discipline of organic chemistry, because all of the old-established reactions need to be reinvestigated for their application in asymmetric synthesis [6]. This has also applied

to the 1,3-dipolar cycloaddition reaction and during the past 15 years there has been enormous interest in asymmetric 1,3-dipolar cycloaddition reactions [7, 8]. Most of the research performed has, however, been on diastereoselective reactions that imply optically active substrates. Unlike the broad application of asymmetric catalysis in carbo- and hetero-Diels-Alder reactions, which has evolved since the mid-nineteen-eighties [9], the use of enantioselective metal catalysts in asymmetric 1,3-dipolar cycloaddition reactions between alkenes and nitrones remained almost unexplored until 1993 [7]. The development of metal-catalyzed asymmetric 1,3-dipolar cycloaddition reactions that has been achieved up to 2000 is compiled in this chapter. After an introduction to the basics of metal-catalyzed 1,3-dipolar cycloaddition subsequent sections are divided according to the metal catalysts applied for the reactions.

6.2
Basic Aspects of Metal-catalyzed 1,3-Dipolar Cycloaddition Reactions

6.2.1
The 1,3-Dipoles

The 1,3-dipoles consist of elements from main groups IV, V, and VI. The parent 1,3-dipoles consist of elements from the second row and the central atom of the dipole is limited to N or O [10]. Thus, a limited number of structures can be formed by permutations of N, C, and O. If higher row elements are excluded twelve allyl anion type and six propargyl/allenyl anion type 1,3-dipoles can be obtained. However, metal-catalyzed asymmetric 1,3-dipolar cycloaddition reactions have only been explored for the five types of dipole shown in Scheme 6.2.

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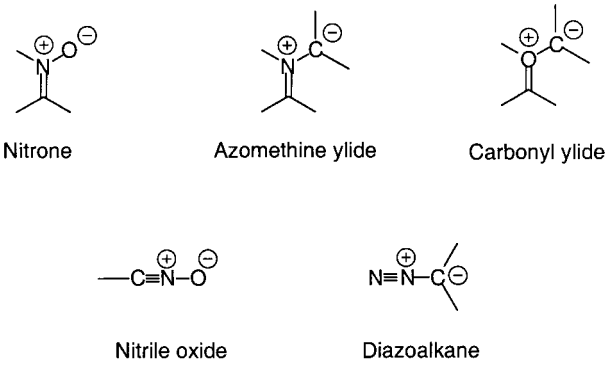


Scheme 6.2

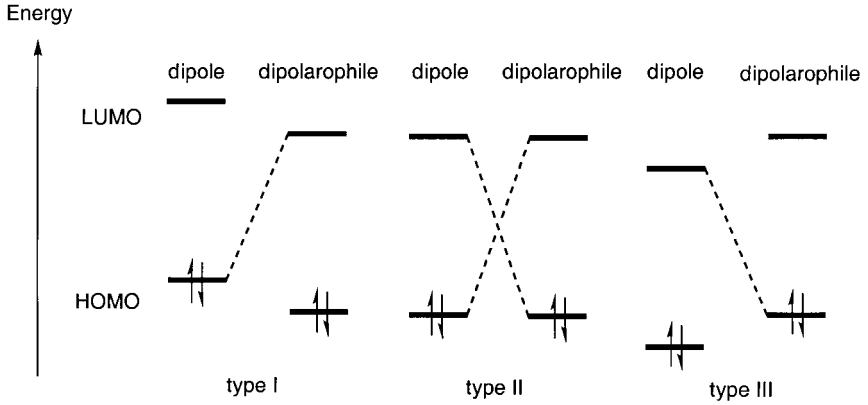
Most studies in this field have been on nitrones. One of the reasons for this is probably because nitrones are readily available compounds that can be obtained from aldehydes, amines, imines, and oximes [2, 11]. Moreover, most acyclic ni-

trones are stable compounds that can be stored under ambient conditions. Cyclic nitrones tend to be less stable, but there are also examples on the application of these. Azomethine ylides are unstable and have to be prepared *in situ*. Several methods have been developed for the synthesis of azomethine ylides, for example proton abstraction from imine derivatives of α-amino acids, thermolysis or photolysis of aziridines and dehydrohalogenation of imonium salts [7, 12]. As with nitrones, azomethine ylides have found broad application in synthesis, but the number of reports on metal-catalyzed asymmetric reactions is very sparse. Carbonyl ylides are a less common type of 1,3-dipole, which have found only limited application in synthesis [13], although access to carbonyl ylides via rhodium carbenes has accelerated the development in this area [14, 15], and over the past three years the first examples of metal-catalyzed asymmetric reactions have appeared. Nitrile oxides on the other hand are, in close competition with nitrones, the most commonly applied 1,3-dipole for the synthesis of five-membered heterocyclic rings [2, 16]. They are easy available from aldoximes or primary nitro compounds, but most nitrile oxides must be prepared *in situ*, because of high reactivity and rapid dimerization. The high reactivity of nitrile oxides is probably one reason for the very few examples of catalytic control of this reaction [7]. Much attention has been devoted to the asymmetric reactions of alkenes with diazoalkanes, but the majority of the work is in relation to cyclopropanation chemistry, which will not be covered here [17]. The only example of a metal-catalyzed asymmetric reaction leading to a stable pyrazole product will be mentioned.

6.2.2
Frontier Molecular Orbital Interactions

The transition state of the concerted 1,3-dipolar cycloaddition reaction is controlled by the frontier molecular orbitals (FMO) of the substrates. The $LUMO_{dipole}$ interacts with the $HOMO_{alkene}$ and the $HOMO_{dipole}$ interacts with the $LUMO_{alkene}$ [3, 18]. Sustman has classified 1,3-dipolar cycloaddition reactions into three types, based on the relative FMO energies between the dipole and the dipolarophile (Scheme 6.3) [19–21]. In type I reactions the dominant FMO interaction is that of the $HOMO_{dipole}$ with the $LUMO_{dipolarophile}$. For type II reactions the similarity of the dipole and dipolarophile FMO energies implies that both HOMO-LUMO interactions are important. Cycloaddition reactions of type III are dominated by the interaction between the $LUMO_{dipole}$ and the $HOMO_{dipolarophile}$.

Reactions of type I are typical for azomethine ylides and carbonyl ylides, whereas 1,3-dipolar cycloaddition reactions of nitrones are normally classified as type II [10]. Reactions of nitrile oxides are also classified as type II, but they are better classified as borderline to type III, since nitrile oxides have relatively low LUMO energies of –11 to –10 eV. It should be taken into account that the classification of a reaction is also dependent on the other reactant. Introduction of electron-donating or electron-withdrawing substituents on the dipole or the dipolarophile can alter the relative FMO energies, and therefore the reaction type, dramatically [20, 21]. The reaction of *N*-methyl-*C*-phenylnitrone with methyl acrylate is



Scheme 6.3

controlled by the $HOMO_{dipole}$-$LUMO_{dipolarophile}$ interaction, whereas the reaction of the same nitrone with methyl vinyl ether is controlled by the $LUMO_{dipole}$-$HOMO_{dipolarophile}$ interaction [11].

The relative FMO energies of the reagents are very important to the catalytic control of the reaction. Let us first have a look at nitrones where this principle has been explored in most detail [7, 22, 23]. To be able to control the stereochemistry of a reaction with a sub-stoichiometric amount of a ligand-metal catalyst it is desirable that large reaction rate accelerations are obtained, to assure that the reaction only takes place in the sphere of the metal and the chiral ligand. The strategy that was applied for the catalytic enhancement of the reaction rate has therefore been to alter the relative energies of the FMO of one of the substrates using chiral Lewis acid complexes [22]. This principle of activation can be applied to the 1,3-dipolar cycloaddition of nitrones with alkenes in two different ways. The reaction between a nitrone and an electron-deficient alkene such as an α,β-unsaturated carbonyl compound is primarily controlled by the interaction between $HOMO_{nitrone}$-$LUMO_{alkene}$ (Scheme 6.4). By the application of a Lewis acid (LA) catalyst which is a strong electron acceptor it has been possible to decrease the energy of the FMO_{alkene} via coordination of the enone to the Lewis acid. As a result of the decreased energy gap between the interacting FMO a rate acceleration of the reaction has been achieved [22].

The other catalytic approach to the 1,3-dipolar cycloaddition reaction is the "inverse electron-demand", in which the nitrone is activated for addition to an electron-rich alkene such as e.g. a vinyl ether (Scheme 6.5). In this scenario the FMO_{alkene} have higher energies than the $FMO_{nitrone}$ and the dominating interaction in the reaction will be $LUMO_{nitrone}$-$HOMO_{alkene}$. In the presence of a Lewis acid catalyst, the nitrone can coordinate to the catalyst, leading to a decrease of the $LUMO_{nitrone}$ energy. The decreased energy gap between the two FMOs responsible for the dominating interaction may lead to an enhanced rate of the 1,3-dipolar cycloaddition reaction. These principles of activation have proven to apply for the 1,3-dipolar cycloaddition reactions involving nitrones and in a single case also for diazoalkanes.

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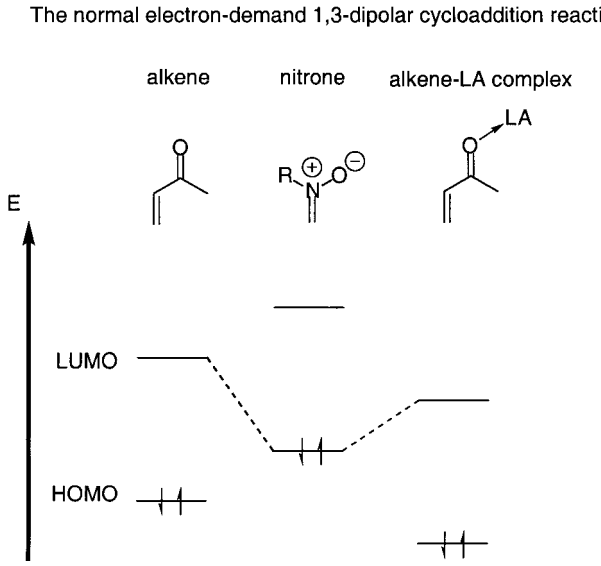
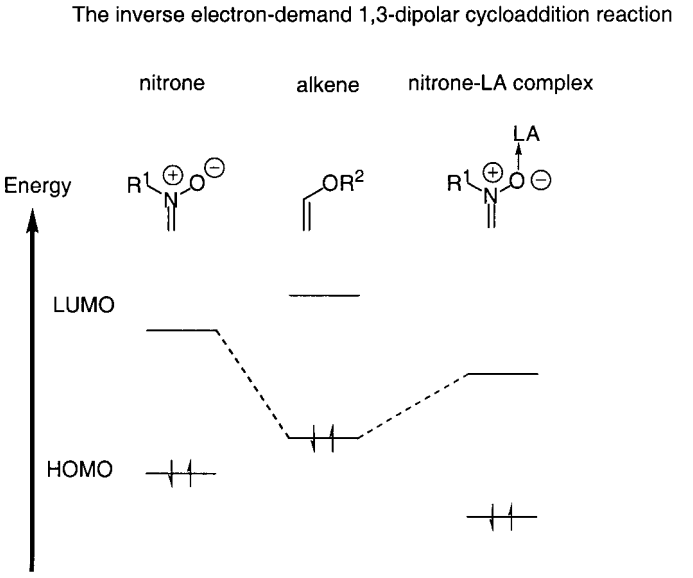


Scheme 6.4



Scheme 6.5

For the reactions of other 1,3-dipoles, the catalyst-induced control of the enantioselectivity is achieved by other principles. Both for the metal-catalyzed reactions of azomethine ylides, carbonyl ylides and nitrile oxides the catalyst is crucial for the in situ formation of the 1,3-dipole from a precursor. After formation the 1,3-dipole is coordinated to the catalyst because of a favored chelation and/or stabiliza-

tion of the substrates, which apparently provide control of the enantioselectivity of the reaction.

6.2.3 The Selectivities of 1,3-Dipolar Cycloaddition Reactions

Three types of selectivity must be considered in 1,3-dipolar cycloaddition reactions – regioselectivity, diastereoselectivity, and enantioselectivity. The regioselectivity is controlled by both steric and electronic effects [18, 24]. For the addition to terminal alkenes the sterically most crowded functionality of the 1,3-dipole tends to add to the terminal carbon atom of the alkene, giving the 5-substituted isomer as shown for nitrones in Scheme 6.6. The steric effects may, however, be overruled by strong electronic effects [2]. In the cycloaddition reaction of electron-rich or electron-neutral alkenes with nitrones, the 5-substituted isomer is obtained. The reaction is primarily controlled by the $LUMO_{dipole}$-$HOMO_{dipolarophile}$ interaction. The $LUMO_{dipole}$ has the largest coefficient at the carbon atom and the $HOMO_{alkene}$ has the largest coefficient at the terminal carbon atom. Thus, the nitrone and alkene combine in a regioselective manner to give the 5-isoxazolidine. This is obviously supported by steric factors. For terminal alkenes with an electron-withdrawing group, the reaction is primarily controlled by the $HOMO_{dipole}$-$LUMO_{dipolarophile}$ interaction. The $HOMO_{dipole}$ has the largest coefficient at the oxygen atom, whereas the $LUMO_{dipolarophile}$ has the largest coefficient at the terminal carbon atom. This favors formation of the 4-isomer, but since steric factors oppose this, a mixture of regioisomers is often obtained [24]. However, in the reaction of nitrones with 1,2-disubstituted alkenes bearing an electron-withdrawing group the steric factor is eliminated, leading to the FMO-controlled regioselectivity of the reaction with the 4-EWG-substituted isomer as the sole product (Scheme 6.6) [2, 11].

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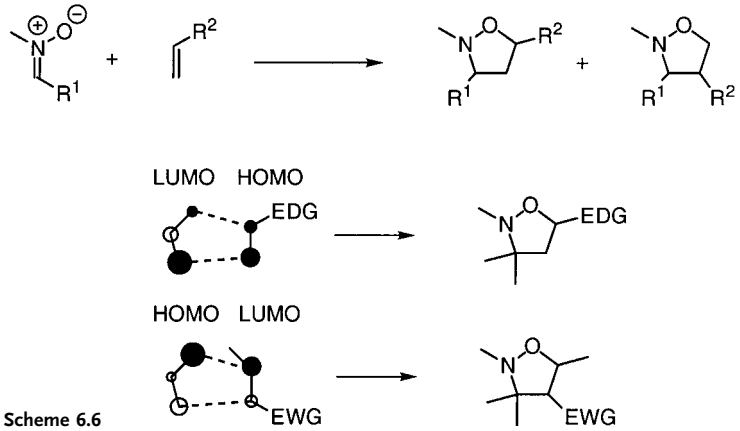
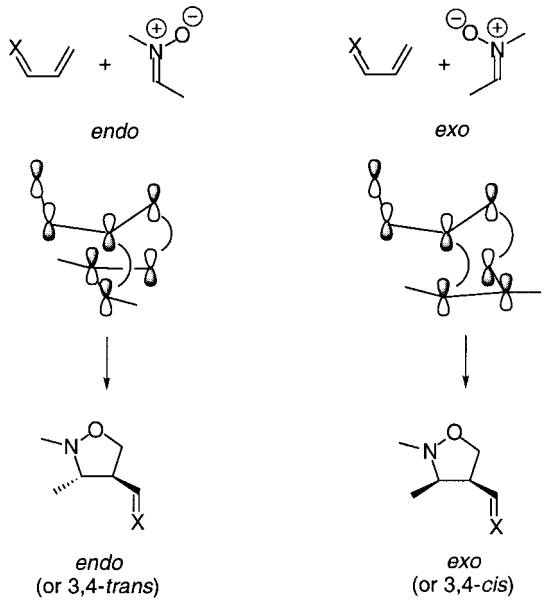


Scheme 6.6

In the 1,3-dipolar cycloaddition reactions of especially allyl anion type 1,3-dipoles with alkenes the formation of diastereomers has to be considered. In reactions of nitrones with a terminal alkene the nitrone can approach the alkene in an *endo* or an *exo* fashion giving rise to two different diastereomers. The nomenclature *endo* and *exo* is well known from the Diels-Alder reaction [3]. The *endo* isomer arises from the reaction in which the nitrogen atom of the dipole points in the same direction as the substituent of the alkene as outlined in Scheme 6.7. However, compared with the Diels-Alder reaction in which the *endo* transition state is stabilized by secondary π-orbital interactions, the actual interaction of the *N*-nitrone p_z-orbital with a vicinal p_z-orbital on the alkene, and thus the stabilization, is small [25]. The *endo*/*exo* selectivity in the 1,3-dipolar cycloaddition reaction is therefore primarily controlled by the structure of the substrates or by a catalyst. It should be noticed that for reactions in which the nitrone can undergo *Z*/*E*-interconversion, the *endo*/*exo* assignment of the products is misleading and therefore *cis* or *trans* should be used instead.



Scheme 6.7

For azomethine ylides and carbonyl ylides, the diastereoselectivity is more complex as the presence of an additional chiral center in the product allows for the formation of four diastereomers. Since the few reactions that are described in this chapter of these dipoles give rise to only one diastereomer, this topic will not be mentioned further here [10].

Finally, there is the enantioselectivity of the 1,3-dipolar cycloaddition reactions. This chapter is limited to describing only the metal-catalyzed asymmetric 1,3-dipolar cycloaddition reactions that involve non-chiral starting materials. The only fac-

tor present for control of the enantioselectivity is therefore the chiral catalyst. The use of chiral metal-ligand complexes to control the enantioselectivity of 1,3-dipolar cycloaddition reactions is the primary focus of this chapter. Therefore the chapter has been divided into sections based on the metal catalysts.

6.3 Boron Catalysts for Reactions of Nitrones

Scheeren et al. reported the first enantioselective metal-catalyzed 1,3-dipolar cycloaddition reaction of nitrones with alkenes in 1994 [26]. Their approach involved *C,N*-diphenylnitrone **1a** and ketene acetals **2**, in the presence of the amino acid-derived oxazaborolidinones **3** as the catalyst (Scheme 6.8). This type of boron catalyst has been used successfully for asymmetric Diels-Alder reactions [27, 28]. In this reaction the nitrone is activated, according to the inverse electron-demand, for a 1,3-dipolar cycloaddition with the electron-rich alkene. The reaction is thus controlled by the $LUMO_{nitrone}$-$HOMO_{alkene}$ interaction. They found that coordination of the nitrone to the boron Lewis acid strongly accelerated the 1,3-dipolar cycloaddition reaction with ketene acetals. The reactions of **1a** with **2a**,**b**, catalyzed by 20 mol% of oxazaborolidinones such as **3a**,**b** were carried out at –78 °C. In some reactions fair enantioselectivities were induced by the catalysts, thus, **4a** was obtained with an optical purity of 74% ee, however, in a low yield. The reaction involving **2b** gave the C-3, C-4-*cis* isomer **4b** as the only diastereomer of the product with 62% ee.

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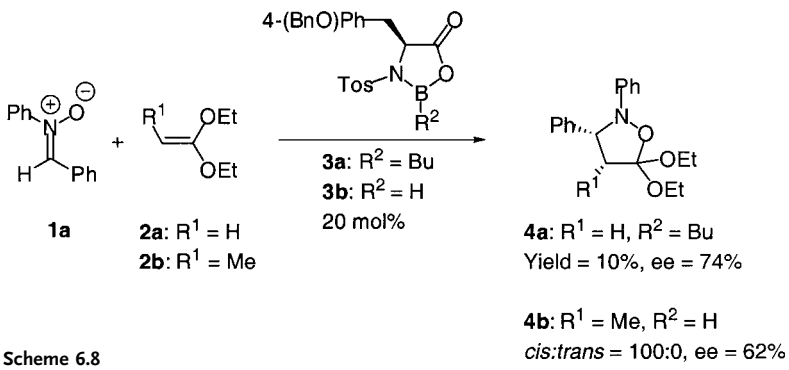
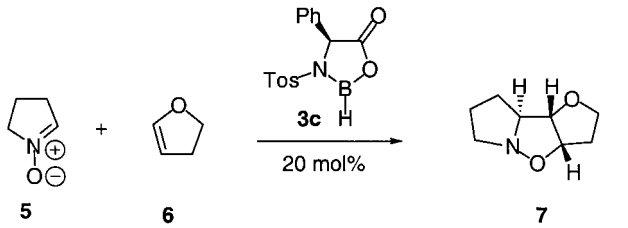


Scheme 6.8

In an extension of this work Scheeren et al. studied a series of derivatives of *N*-tosyl-oxazaborolidinones as catalysts for the 1,3-dipolar cycloaddition reaction of **1** with **2b** [29]. The addition of a co-solvent appeared to be of major importance. Catalyst **3b** was synthesized from the corresponding amino acid and $BH_3 \cdot THF$, hence, THF was present as a co-solvent. In this reaction (–)-**4b** was obtained with 62% ee. If the catalyst instead was synthesized from the amino acid and

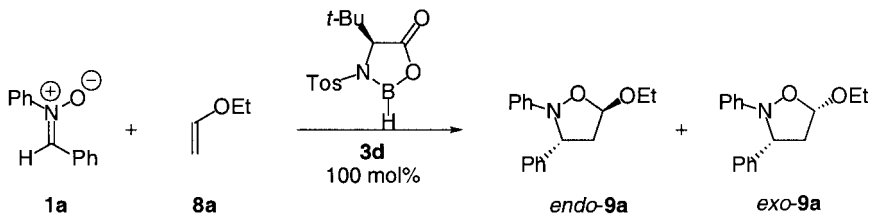
$BH_3 \cdot SMe_2$, and diphenyl ether was added, a remarkable reversal of the enantioselectivity of the reaction occurred, since (+)-**4b** was now obtained as the major isomer. Furthermore, the ee in this approach was improved to be 79%.

In a more recent work the same research group has applied cyclic and acyclic vinyl ethers in the oxazaborolidinone-catalyzed 1,3-dipolar cycloaddition reaction with nitrones [30]. The reaction between nitrone **5** and 2,3-dihydrofuran **6** with 20 mol% of the phenyl glycine-derived catalyst **3c**, gave the product **7** in 56% yield as the sole diastereomer, however, with a low ee of 38% (Scheme 6.9).



Scheme 6.9

In an analogous study by Meske, the impact of various oxazaborolidinone catalysts for the 1,3-dipolar cycloaddition reactions between acyclic nitrones and vinyl ethers was studied [31]. Both the diastereo- and the enantioselectivities obtained in this work were low. The highest enantioselectivity was obtained by the application of 100 mol% of the *tert*-butyl-substituted oxazaborolidinone catalyst **3d** [27, 32] in the 1,3-dipolar cycloaddition reaction between nitrone **1a** and ethyl vinyl ether **8a** giving *endo*-**9a** and *exo*-**9a** in 42% and 27% isolated yield, respectively, with up to 20% ee for *endo*-**9a** as the best result (Scheme 6.10).

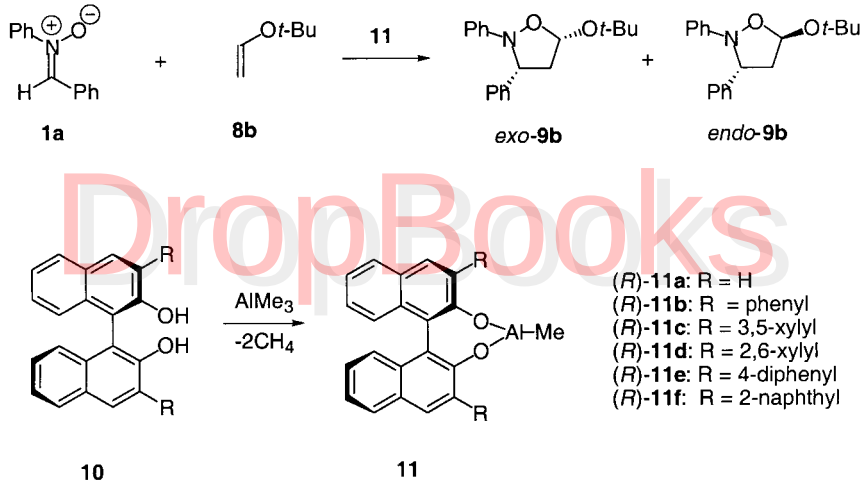


Scheme 6.10

6.4
Aluminum Catalysts for Reactions of Nitrones

As for boron catalysts, the aluminum catalysts have exclusively been applied for the inverse electron-demand 1,3-dipolar cycloaddition between alkenes and nitrones. The first contribution to this field was published by Jørgensen et al. in

1999 [23]. The initial catalytic experiments were performed using the AlMe-BINOL catalyst **11a**, that was simply synthesized by mixing the chiral ligand 1,1-binaphthol (BINOL) **10a** with $AlMe_3$ (Scheme 6.11). This catalyst was applied for the reaction between nitrone **1a** and vinyl ether **8b**. A large rate enhancement was observed by using this catalyst, however, the selectivity of the reaction was rather disappointing. An *exo*/*endo* ratio of 73 : 27 was obtained and the *exo* product was formed with a low ee of <5%. As a part of these studies a new method for the synthesis of 3,3′-aryl-substituted BINOL ligands **10b–f** was developed [33]. The introduction of substituents on the ligands 3,3′-position as in catalysts **11b–f** led to a remarkable improvement of the selectivities when these catalysts were applied in the reaction of **1a** with **8b** (Scheme 6.11). Especially, complex **11b** possessed the desired properties as the reaction performed in the presence 20 mol% of this catalyst was completed to give *exo*-**9b** as the only observable diastereomer and the enantioselectivity of this product was 89% ee.



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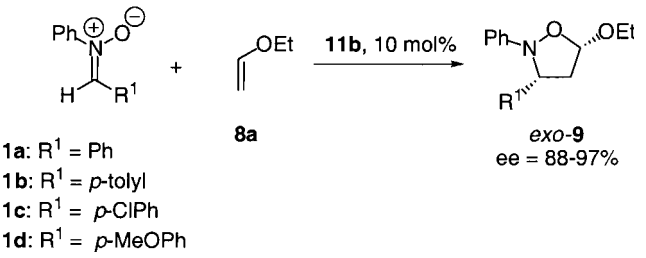
Scheme 6.11

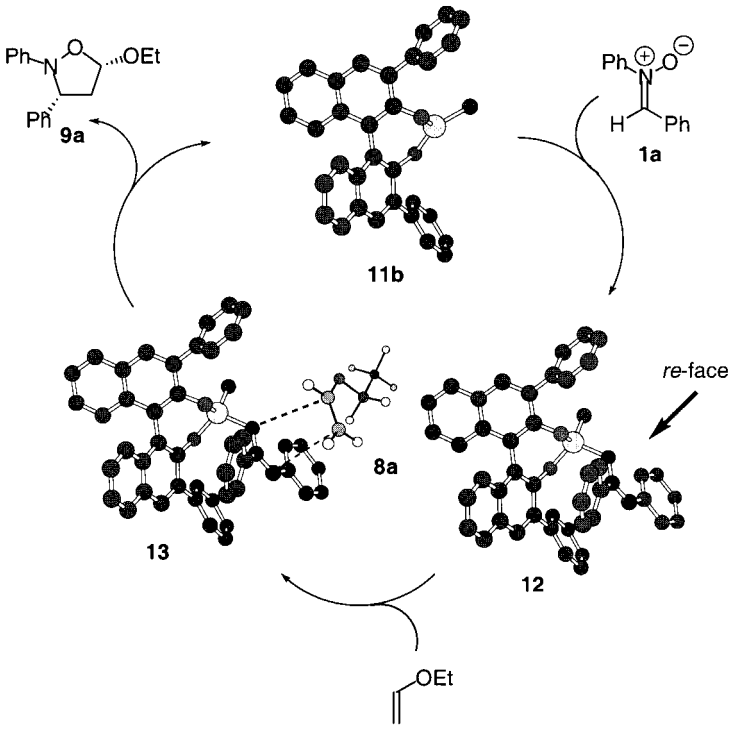
Further improvement of the reaction was achieved by applying ethyl vinyl ether **8a** in the reaction instead of **8b** (Scheme 6.12). The reactions between a series of nitrones **1a–d** with **8a** catalyzed by 10 mol% of **11b** all proceeded to give the corresponding products **9** with excellent *exo* selectivity and with enantioselectivity of 88–97% ee in all cases [23].

A model for the mechanism of the highly enantioselective AlMe-BINOL-catalyzed 1,3-dipolar cycloaddition reaction was proposed as illustrated in Scheme 6.13. In the first step nitrone **1a** coordinates to the catalyst **11b** to form intermediate **12**. In intermediate **13**, which is proposed to account for the absolute stereoselectivity of this reaction, it is apparent that one of the faces of the nitrone, the *si* face, is shielded by the ligand whereas the *re* face remains available



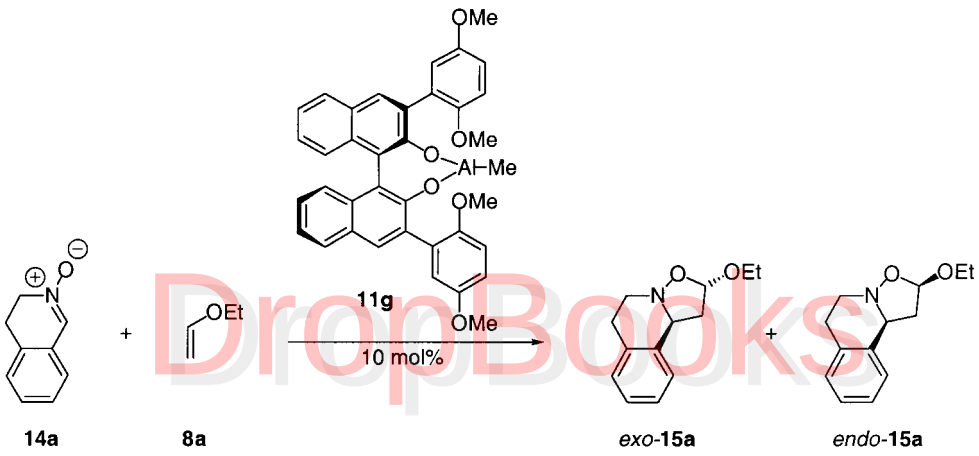
Scheme 6.12

for reaction with ethyl vinyl ether **8a** as shown in the next step. The high *exo* selectivity may also be explained by the model. As it appears from the step in which **8a** approaches the nitrone-catalyst complex **13**, the ethoxy moiety of **8a** is pointing away from the nitrone *N*-phenyl group which leads to formation of the *exo* isomer of the product **9a**. The assignment of the absolute configuration of the product was in full agreement with the *re* face selectivity proposed in this model [23].



Scheme 6.13

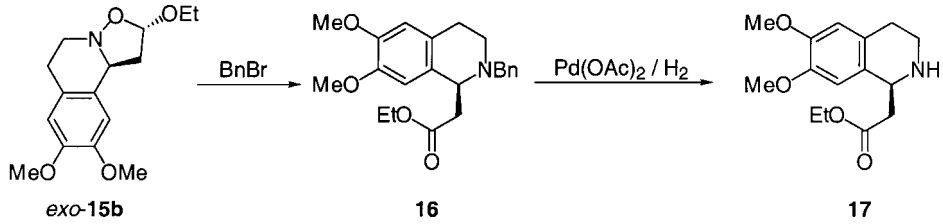
The above described reaction has been extended to the application of the AlMe-BINOL catalyst to reactions of acyclic nitrones. A series chiral AlMe-3,3′-diaryl-BINOL complexes **11b–f** was investigated as catalysts for the 1,3-dipolar cycloaddition reaction between the cyclic nitrone **14a** and ethyl vinyl ether **8a** [34]. Surprisingly, these catalysts were not sufficiently selective for the reactions of cyclic nitrones with ethyl vinyl ether. Use of the tetramethoxy-substituted derivative **11g** as the catalyst for the reaction significantly improved the results (Scheme 6.14). In the presence of 10 mol% **11g** the reaction proceeded in a mixture of CH_2Cl_2 and petroleum ether to give the product **15a** in 79% isolated yield. The diastereoselectivity was the same as in the acyclic case giving an excellent ratio of *exo*-**15a** and *endo*-**15a** of >95 : <5, and *exo*-**15a** was obtained with up to 82% ee.



Scheme 6.14

The high enantioselectivity of the *exo* product opens up a new and readily accessible route to an enantioselective synthesis of interesting isoquinoline alkaloids (Scheme 6.15) [35]. The tricyclic isoxazolidine *exo*-**15b** was obtained from the 1,3-dipolar cycloaddition reaction as the pure *exo* isomer and with 58% ee [34]. As shown in Scheme 6.15 the *exo* product from the 1,3-dipolar cycloaddition was converted into **17** in two steps without racemization at the chiral center. In addition to the illustrated synthesis, the 6,7-dimethoxy-derived isoxazolidine *exo*-**15b** is a very useful precursor for the synthesis of naturally occurring isoquinoline alkaloids [36–40].

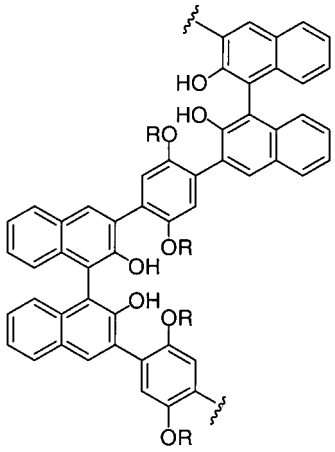
A new type of rigid polymer of 1,1-binaphthols was developed recently [41–43]. The 3,3′-crosslinked polymeric binaphthol ligand **18** in combination with $AlMe_3$ was applied as the catalyst for the 1,3-dipolar cycloaddition (Scheme 6.16) [44]. Very high selectivities were obtained when the aluminum catalyst of **18** (20 mol%) was applied to the 1,3-dipolar cycloaddition reaction between nitrone **1a** and alkene **8a**. The only observable diastereomer resulting from the reactions was *exo*-**9a**



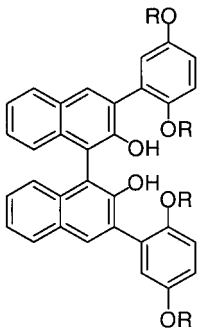
exo-**15b** **16** **17**

Scheme 6.15

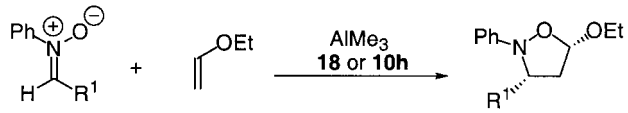
and it was obtained with an enantioselectivity as high as 99% ee. One of the advances of using a polymeric catalyst is the easy removal and recovery of the ligand from the reaction. Upon completion of the reaction the catalyst was hydrolyzed and the ligand precipitated by addition of methanol. After evaporation of the solvent and the excess of **8a**, the pure product *exo*-**9a** was isolated in 97% yield. Similar excellent selectivities were obtained for reactions of other nitrones.



18 R = C_6H_{13}



10h R = C_6H_{13}



1a: R^1 = Ph
1b: R^1 = *p*-tolyl
1c: R^1 = *p*-ClPh

8a

exo-**9**
de >96%
ee = 94-99%

Scheme 6.16

Another important advantage of using the polymeric ligand **18** is, in addition to the easy purification of the product, that the ligand can be isolated and re-used after the simple precipitation procedure. In this manner a sample of the polymeric ligand was isolated and re-used in four consecutive reactions of nitrone **1a** and ethyl vinyl ether **8a**. Both yield and enantioselectivity of *exo*-**9a** showed only slight decreases after the ligand had been re-used. The slight decrease was ascribed to the loss of small amounts of the ligand during the recycling procedure [44].

The monomeric counterpart **10h** of the polymeric ligand was also synthesized and applied in the 1,3-dipolar cycloaddition reaction in order to compare the properties with the polymeric ligand. When **10h** in combination with $AlMe_3$ (10 mol%) was used as the catalyst, the reaction between nitrones **1a–c** and ethyl vinyl ether **8a** the reaction proceeded at 0 °C to give the pure *exo*-**9** in yields ranging from 76–93%. The enantioselectivities of the reactions were very high at 94–99% ee, and thus comparable to the results obtained using the polymeric ligand.

6.5 Magnesium Catalysts for Reactions of Nitrones

Before the first publication on chiral magnesium catalysts for 1,3-dipolar cycloaddition reactions in 1995, there had been several studies on the impact of non-chiral magnesium salts on the diastereoselectivities in cycloaddition reactions of both nitrones [45–47], and nitrile oxides [48] with allylic alcohols. In the first [25] and also the following [49–51] publications on chiral magnesium catalysts, chiral bisoxazolines (BOX) were applied as the ligand for magnesium. The MgX_2-Ph-BOX catalyst **20** (X = I), proved to be a useful catalyst for the 1,3-dipolar cycloaddition between **1** and **19a**,**b** when it was activated by the addition of I_2 (Scheme 6.17) [25]. Furthermore, the reaction had to be performed in the presence of molecular sieves (MS) 4 Å. In the presence of 10 mol% of **20** (X = I) the reaction proceeded with good to high *endo* selectivity and the *endo* isomer was obtained in an ee of up to 82%. In this case it is the bidentate and electron-deficient alkenoyloxazolidinones that are activated by the catalyst for reaction with the nitrone. Thus, in contrast with the reactions catalyzed by the monodentate boron and aluminum catalysts the magnesium-catalyzed reaction proceeds according to the normal electron-demand.

A rather unexpected discovery was made in connection to these investigations [49]. When the 1,3-dipolar cycloaddition reaction of **1a** with **19b** mediated by catalyst **20** (X = I) was performed in the absence of MS 4 Å a remarkable reversal of enantioselectivity was observed as the opposite enantiomer of *endo*-**21** was obtained (Table 6.1, entries 1 and 2). This had not been observed for enantioselective catalytic reactions before and the role of molecular sieves cannot simply be ascribed to the removal of water by the MS, since the application of MS 4 Å that were presaturated with water, also induced the reversal of enantioselectivity (Table 6.1, entries 3 and 4). Recently, Desimoni et al. also found that in addition to the presence of MS in the MgX_2-Ph-BOX-catalyzed 1,3-dipolar addition shown in Scheme 6.17, the counter-ion for the magnesium catalyst also strongly affect the absolute stereoselectivity of the reac-

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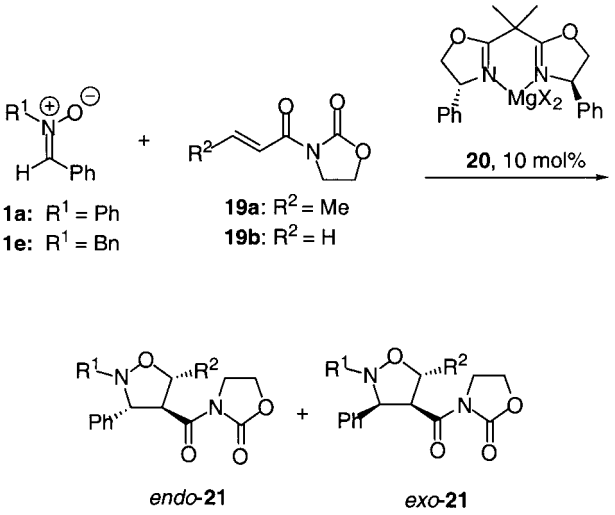

Scheme 6.17

tion [50, 51]. They applied MgX_2-Ph-BOX **20** (X = ClO_4) and MgX_2-Ph-BOX **20** (X = OTf) complexes and compared the results with the MgX_2-Ph-BOX catalyst **20** (X = I). It was observed that both in the presence and in the absence of MS, the catalyst **20** (X = ClO_4) gave the opposite absolute configuration of the product compared to the reaction of catalyst **20** (X = I) (Table 6.1, entries 5 and 6). For catalyst **20** (X = OTf), the reaction was racemic in the presence of MS, whereas a high enantioselectivity of 86% ee was obtained in the absence of additives. The absolute configuration of the product of the reaction catalyzed by **20** (X = OTf) in the absence of MS was

Tab. 6.1 Dependence of absolute stereoselectivity on molecular sieves and counter ion in the reaction of **1a** with **19b** catalyzed by 10 mol% MgX_2-Ph-BOX catalysts **20**

Entry	*MgX_2-counter-ion*	*Additive*	*T (°C)*	*endo/exo (%)*	*ee endo (%)*	*Absolute induction*	*Refs.*
1	I	MS[a] 4 Å	–78	73:27	82	3*S*, 4*R*	49
2	I	–	–78	100:0	48	3*R*, 4*S*	49
3	I	H_2O[b]	–78	90:10	36	3*R*, 4*S*	49
4	I	MS 4 Å, H_2O[c]	–78	95:5	36	3*S*, 4*R*	49
5	ClO_4	MS 4 Å	–15	70:30	70	3*R*, 4*S*	50, 51
6	ClO_4	–	–15	95:5	48	3*S*, 4*R*	50, 51
7	OTf	MS 4 Å	–15	56:44[d]	2	–	50, 51
8	OTf	–	–15	97:3	86	3*S*, 4*R*	50, 51

a) Molecular sieves
b) 20 mol% H_2O relative to the catalyst
c) MS 4 Å saturated with H_2O in CH_2Cl_2 with a stable content of 18 mol% H_2O relative to the catalyst
d) Mixture of regioisomers obtained

similar to that obtained with **20** (X = ClO_4) catalyst and opposite to that obtained with **20** (X = I) (entries 2, 6 and 8) [50].

6.6 Titanium Catalysts for Reactions of Nitrones and Diazoalkanes

Several titanium(IV) complexes are efficient and reliable Lewis acid catalysts and they have been applied to numerous reactions, especially in combination with the so-called TADDOL ($\alpha,\alpha,\alpha',\alpha'$-tetraaryl-1,3-dioxolane-4,5-dimethanol) (**22**) ligands [53–55]. In the first study on normal electron-demand 1,3-dipolar cycloaddition reactions between nitrones and alkenes, which appeared in 1994, the catalytic reaction of a series of chiral $TiCl_2$-TADDOLates on the reaction of nitrones **1** with alkenoyloxazolidinones **19** was developed (Scheme 6.18) [56]. These substrates have turned out be the model system of choice for most studies on metal-catalyzed normal electron-demand 1,3-dipolar cycloaddition reactions of nitrones as it will appear from this chapter. When 10 mol% of the catalyst **23a** was applied in the reaction depicted in Scheme 6.18 the reaction proceeded to give a yield of up to 94% ee after 20 h. The reaction led primarily to *exo*-**21** and in the best case an *endo*/*exo* ratio of 10:90 was obtained. The chiral information of the catalyst was transferred with a fair efficiency to the substrates as up to 60% ee of one of the isomers of *exo*-**3** was obtained [56].

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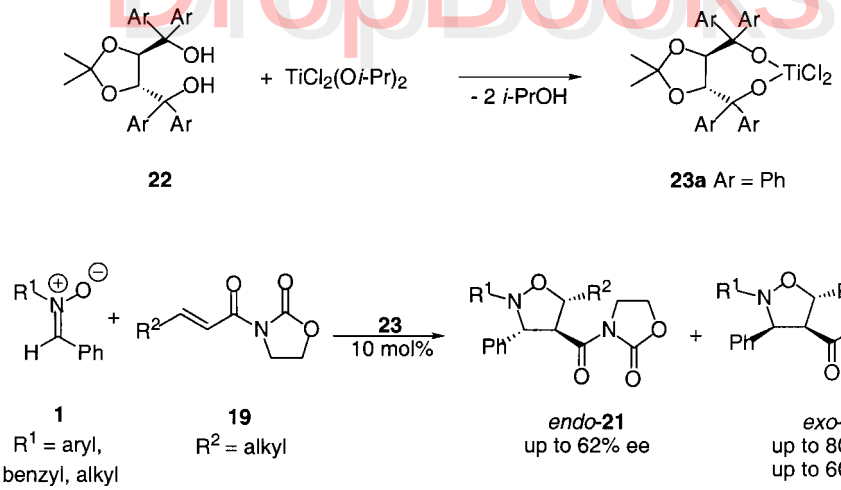
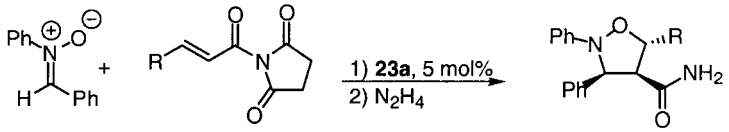


Scheme 6.18

In most $TiCl_2$-TADDOLate-catalyzed Diels-Alder and 1,3-dipolar cycloaddition reactions oxazolidinone derivatives are applied as auxiliaries for the alkenoyl moiety in order to obtain the favorable bidentate coordination of the substrate to the catalyst

[57]. In a more recent study on 1,3-dipolar cycloaddition reactions the use of succinimide instead of the oxazolidinone auxiliary was introduced (Scheme 6.19) [58]. The succinimide derivatives **24a**,**b** are more reactive towards the 1,3-dipolar cycloaddition reaction with nitrone **1a** and the reaction proceeds in the absence of a catalyst. In the presence of $TiCl_2$-TADDOLate catalyst **23a** (5 mol%) the reaction of **1a** with **24a** proceeds at –20 to –10 °C, and after conversion of the unstable succinimide adduct into the amide derivative, the corresponding product **25** was obtained in an *endo*/*exo* ratio of <5:>95. Additionally, the enantioselectivity of the reaction of 72% ee is also an improvement compared to the analogous reaction of the oxazolidinone derivative **19**. Similar improvements were obtained in reactions of other related nitrones with **24a** and **b**.

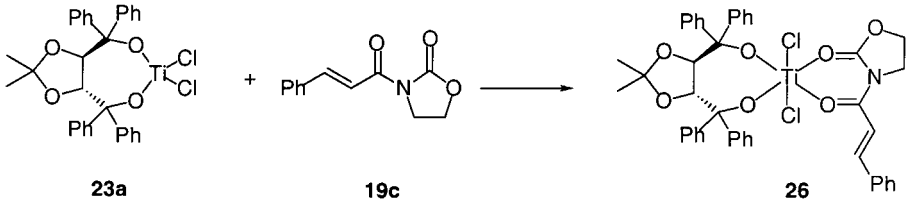


1a **24a**: R = Me **24b**: R = Pr *exo*-**25** up to >90% de up to 72% ee

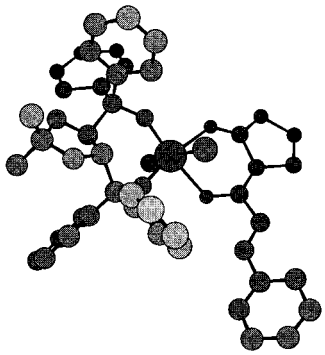
Scheme 6.19

In connection with the first investigations of the $TiCl_2$-TADDOLate-catalyzed 1,3-dipolar cycloaddition reactions between nitrones and alkenoyloxazolidinones, a complex between the chiral titanium catalyst and the alkene substrate **19c** was isolated (Scheme 6.20) [59]. The crystalline compound **26** was characterized by X-ray crystallography and the X-ray structure showed that the oxazolidinone is coordinated to the titanium center in a bidentate fashion as expected. The four oxygen atoms, two from the chiral ligand and two from **19c**, are located in a plane around the titanium center. The two chloride ligands are located in the apical positions. This crystal structure is a highly valuable verification of how the mechanism of the catalytic activation is operating. To some extent, information can also be derived about how one of the faces of the alkene is shielded by the ligand leading to the asymmetric addition of the nitrone to the opposite face of the alkene. However, there are several other possible arrangements of the ligands around the titanium center, and whether structure **26** actually represents the reactive intermediate in the addition to the double bond has been the subject of some dispute [60–64].

On the basis of examination of intermediate **26**, investigations on the impact on the *endo*/*exo* selectivity in the 1,3-dipolar cycloaddition reaction by changing the chloride ligands in the $TiCl_2$-TADDOLate catalyst **23a** to bulkier groups were performed [65]. The results of reactions between **1a** and **19a** in the presence of various TiX_2-TADDOLate catalysts are listed in Table 6.2 (Schemes 6.18 and 6.21). By the application of **23b**, which is the bromide analog to **23a**, the diastereoselectivity changes (entry 2). This reaction proceeds with a low *endo* selectivity. Using the triflate analog **23c**, leads to an *endo*-selective reaction (entry 3). Unfortunately, this reaction was ra-



23a **19c** **26**



X-Ray structure of **26**

Scheme 6.20

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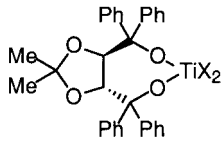
cemic. The reaction of **1a** and **19a** in the presence of 10 mol% of the bulky tosylate analog **23d** is very slow, however, by the application of 50 mol% of catalyst **23d**, a high conversion is obtained after 48 h (entry 4). The *endo* selectivity of this reaction is excellent, and this was the first example of a metal-catalyzed 1,3-dipolar cycloaddition reaction between nitrones and alkenes proceeding with more than 90% ee.



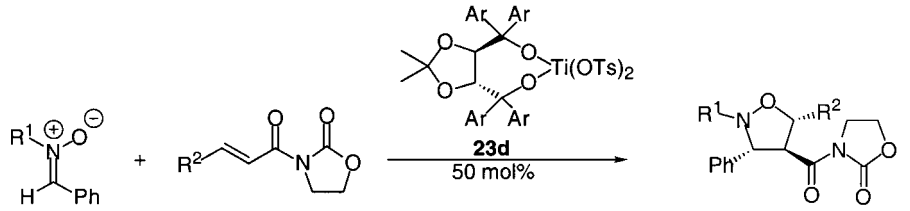
23a: X = Cl
23b: X = Br
23c: X = OTf
23d: X = OTs

Scheme 6.21

On the basis of this successful application of **23d**, this catalyst was applied in a series of reactions (Scheme 6.22). For all eight reactions of nitrones **1** and alkenes **19** in which **23d** was applied as the catalyst, diastereoselectivities >90% de were observed, and most remarkably >90% ee is obtained for all reactions involving a nitrone with an aromatic R^1 substituent whereas reactions with *N*-benzyl and *N*-alkyl nitrones led to lower enantioselectivities [65].

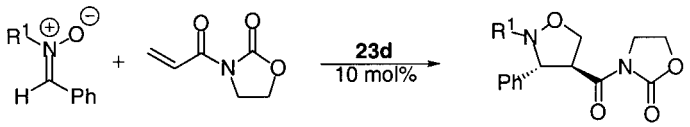
Tab. 6.2 Application of TiX_2-TADDOLate as catalyst for the 1,3-dipolar cycloaddition reaction between **1a** and **19a**

Entry	*Catalyst*	*Catalyst amount*	*Conversion (time)*	*endo/exo*	*ee endo (exo) (%)*
1	**23a**	10	98% (48)	10:90	62 (60)
2	**23b**	10	98% (20)	64:36	76 (64)
3	**23c**	10	73% (20)	79:21	0
4	**23d**	50	99% (48)	>95:<5	93



Scheme 6.22

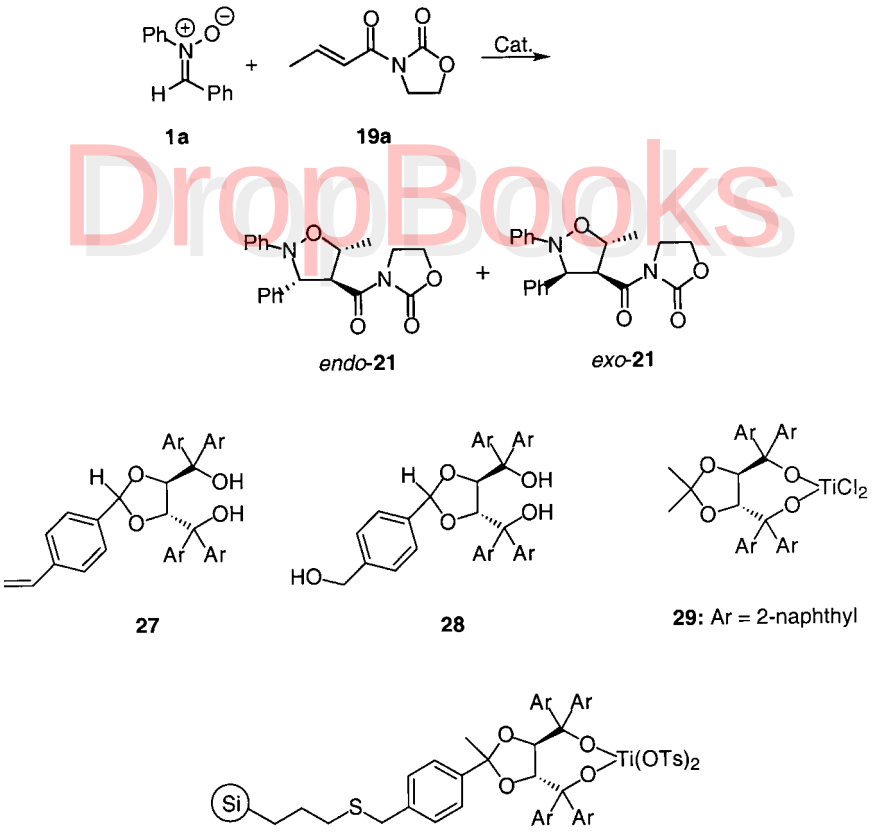
The TiX_2-TADDOLate-catalyzed 1,3-dipolar cycloaddition reactions were extended to include an acrylate derivative [66]. In the absence of a catalyst, the reaction between nitrones **1** and acryloyl oxazolidinone **19b** proceeded to give a mixture all eight regio- and stereoisomers (Scheme 6.23). However, application of in this case only 10 mol% of $Ti(OTs)_2$-TADDOLate **23d** as catalyst for the reaction of various nitrones **1** with alkene **19b**, led to complete regioselectivity and high *endo* selectivity in the reaction and the *endo* products **21** were obtained with 48–70% ee (Scheme 6.23) [66].



Scheme 6.23

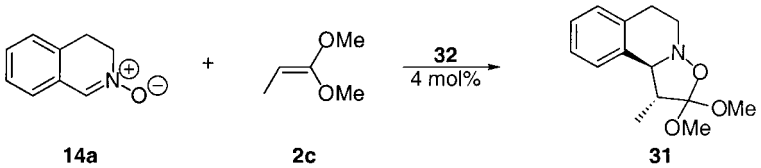
Seebach et al., who first developed the TADDOL ligands [53, 67], have also developed a number of polymer- and dendrimer-bound $TiCl_2$-TADDOLate catalysts derived from the monomeric TADDOLs [68]. Application of 10 mol% of this type of catalysts, derived from polymers and dendrimers of **27** and **28**, respectively, in the

reaction between nitrone **1a** and alkene **19a** led to *endo*/*exo* ratios between 18:82 and 8:92 and enantioselectivities of up to 56% ee (Scheme 6.24). The enantioselectivities are thus slightly decreased compared to the similar reactions of the homogeneous catalysts [56, 68]. They also made a study of the relationship between the enantiomeric purity of the ligand of the homogeneous catalyst **29**, and the products obtained in both the 1,3-dipolar cycloaddition reaction between **1a** and **19a** and in the Diels-Alder reaction of **19a** with cyclopentadiene. Surprisingly, the 1,3-dipolar cycloaddition shows a linear relationship, whereas the Diels-Alder reaction shows a positive non-linear relationship. In a recent work Seebach et al. have studied the use and re-use of $Ti(OTs)_2$-TADDOLate catalysts immobilized on porous silica gel [69]. The selectivity obtained in the 1,3-dipolar cycloaddition between nitrone **1a** and **19a** catalyzed by **30**, was only slightly lower compared to the corresponding homogeneous reaction [65]. The same batch of the ligand in **30** could be used in four consecutive reactions with no significant loss of activity, when the ligand was carefully washed between the reactions [69].

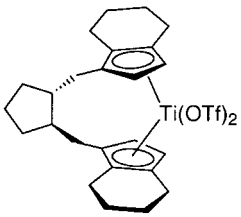


Scheme 6.24

A quite different type of titanium catalyst has been used in an inverse electron-demand 1,3-dipolar cycloaddition. Bosnich et al. applied the chiral titanocene-$(OTf)_2$ complex **32** for the 1,3-dipolar cycloaddition between the cyclic nitrone **14a** and the ketene acetal **2c** (Scheme 6.25). The reaction only proceeded in the presence of the catalyst and a good *cis*/*trans* ratio of 8:92 was obtained using catalyst **32**, however, only 14% ee was observed for the major isomer [70].



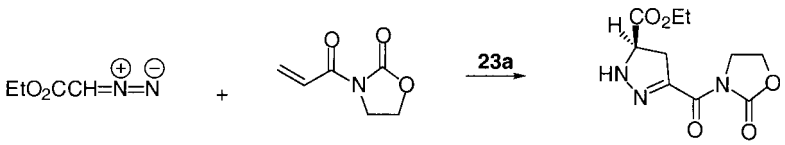
14a **2c** **31**



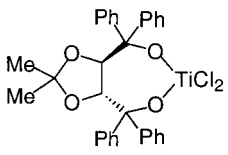
32

Scheme 6.25

The normal electron-demand principle of activation of 1,3-dipolar cycloaddition reactions of nitrones has also been tested for the 1,3-dipolar cycloaddition reaction of alkenes with diazoalkanes [71]. The reaction of ethyl diazoacetate **33** with **19b** in the presence of a $TiCl_2$-TADDOLate catalyst **23a** afforded the 1,3-dipolar cycloaddition product **34** in good yield and with 30–40% ee (Scheme 6.26).



33 **19b** **34**
ee = 30-40%



23a

Scheme 6.26

6.7
Nickel Catalysts for Reactions of Nitrones

In 1998 Kanemasa et al. published the structure of a new dibenzofuranyl 2,2′-bis-oxazoline (DBFOX) which has proved to be an excellent ligand for a variety of Lewis acids [72]. The catalytic reactions that have been developed using this type of Lewis acid-DBFOX complexes, which include some new important catalytic 1,3-dipolar cycloaddition reactions of nitrones, nitronates and diazo compounds are described in a separate chapter in this book. Thus, in this section only the work on 1,3-dipolar cycloaddition reactions that has been published at the present will be described [73]. In this work a $Ni(ClO_4)_2$-PhDBFOX complex **35** is applied as the chiral catalyst (Scheme 6.27). Quite remarkably this Lewis acid catalyst can be formed from the aqueous $Ni(ClO_4)_2 \cdot 6H_2O$ salt and the ligand. The water could be removed by the addition of MS 4 Å. The reaction between different nitrones **1** and crotonoyloxazolidinone **19a** proceeded in the presence of 10 mol% of the dicationic nickel complex **35** as the catalyst. Although long reaction times were required to obtain good yields, the reactions proceeded, in most cases, with very high *endo* selectivities and, in several cases, >99% ee of the *endo* products **21** was obtained. So far this catalyst is undoubtedly the most selective catalyst for the normal electron-demand 1,3-dipolar cycloaddition reaction between nitrones and alkenes, especially, with respect to the enantioselectivity of the reaction [73].

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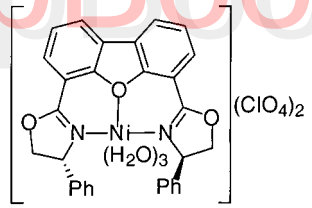
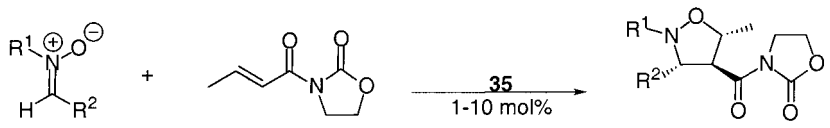


35

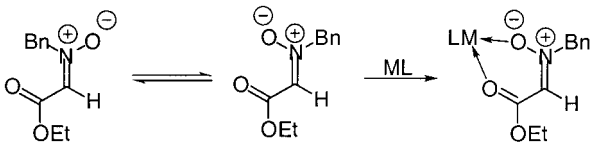


1 **19a** ***endo*-21** up to >99% ee

Scheme 6.27

6.8
Copper Catalysts for Reactions of Nitrones

The enantioselective inverse electron-demand 1,3-dipolar cycloaddition reactions of nitrones with alkenes described so far were catalyzed by metal complexes that favor a monodentate coordination of the nitrone, such as boron and aluminum complexes. However, the glyoxylate-derived nitrone **36** favors a bidentate coordination to the catalyst. This nitrone is a very interesting substrate, since the products that are obtained from the reaction with alkenes are masked *α*-amino acids. One of the characteristics of nitrones such as **36**, having an ester moiety in the *α* position, is the swift *E*/*Z* equilibrium at room temperature (Scheme 6.28). In the crystalline form nitrone **36** exists as the pure *Z* isomer, however, in solution nitrone **36** have been shown to exists as a mixture of the *E* and *Z* isomers. This equilibrium could however be shifted to the *Z* isomer in the presence of a Lewis acid [74].

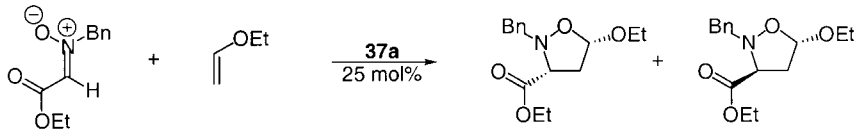


Scheme 6.28

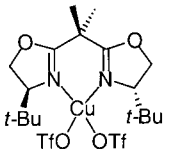
To control the stereochemistry of 1,3-dipolar cycloaddition reactions involving this type of nitrone, chiral copper catalysts were applied [74]. For the 1,3-dipolar cycloaddition reaction of **36** was chosen the electron-rich ethyl vinyl ether **8a** as the dipolarophile (Scheme 6.29). In the absence of a catalyst the reaction of **36** with **8a** in CH_2Cl_2 gave a low conversion of 40% after 66 h and a 24 : 76 mixture of *exo*-**38a** and *endo*-**38a** was obtained. A series of chiral catalysts was investigated for the reaction and the $Cu(OTf)_2$-BOX complex **37a** was found to be the most suitable catalyst for this reaction. In the presence of 25 mol% of **37a** the reaction proceeded at rt in CH_2Cl_2 to give a conversion of 98% after only 8.5 h. The diastereoselectivity of the reaction was improved to an *exo*/*endo* ratio of 84 : 16 and, as the most significant result, *exo*-**38a** was obtained with 89% ee. By changing the solvent to toluene the diastereoselectivity of the reaction was slightly lowered, but the enantioselectivity was improved to 93% ee [74].

A model for the intermediate consisting of substrates **36** and **8a** coordinated to catalyst **37a** was proposed as shown in Scheme 6.30 [74]. In the model **39** the two triflate ligands are dissociated from copper. The ligands are arranged around copper as a trigonal bipyramid and it should be noted that in this model the oxygen atom of the vinyl ether **8a** also coordinates to the metal center. However, another tetrahedral intermediate consisting of only the catalyst and the nitrone could also account for the absolute selectivity of the reaction.

Another rather peculiar asymmetric copper-catalyzed reaction was published some years earlier by Miura et al. [75]. The reaction is outlined in Scheme 6.31

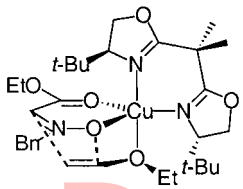


36 **8a** *exo*-**38a** *endo*-**38a**



37a

Scheme 6.29



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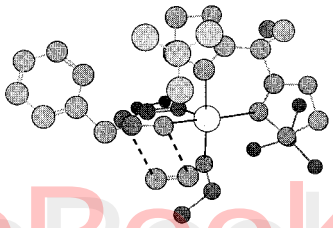

39

Scheme 6.30

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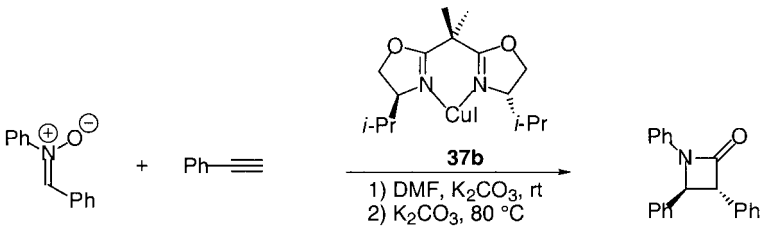
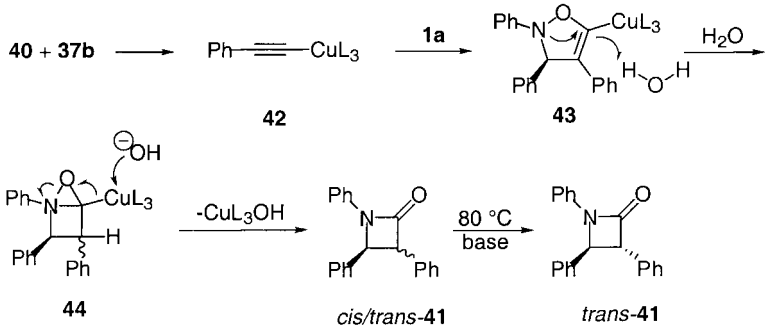
and it involves the reaction of nitrone **1a** with phenylacetylene **40**, catalyzed by CuI–*i*-Pr–BOX **37b**. The product of this reaction is not a 1,3-dipolar cycloaddition adduct, rather it is the azetidone **41**. By using 1 equivalent of the chiral catalyst the *trans* isomer **41** is obtained in 54 yield with 68% ee. If the catalyst loading is lowered to 10 mol% CuI and 20 mol% ligand the selectivity decreases to 57% ee.



1a **40** **41**

Scheme 6.31

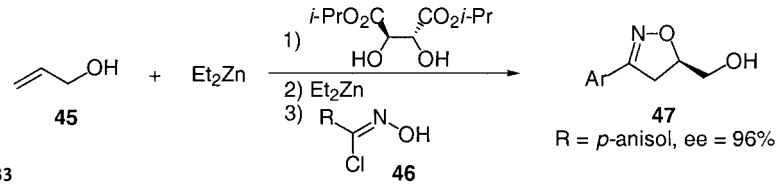
A mechanism for this reaction has been proposed [75]. The first key intermediate in the reaction is the copper(I) acetylide **42**. The additional ligand may be solvent or H_2O. The acetylene moiety in **42** is activated for a 1,3-dipolar cycloaddition with the nitrone to give intermediate **43**, with introduction of chirality in the product. A possible route to *cis*/*trans*-**41** might be via intermediate **44**. Finally, the *cis* isomer is isomerized into the thermally more stable *trans*-**41**. It should be mentioned that the mechanism outlined in Scheme 6.32 was originally proposed for a racemic version of the reaction to which water was added.



Scheme 6.32

6.9
Zinc Catalysts for Reactions of Nitrones and Nitrile Oxides

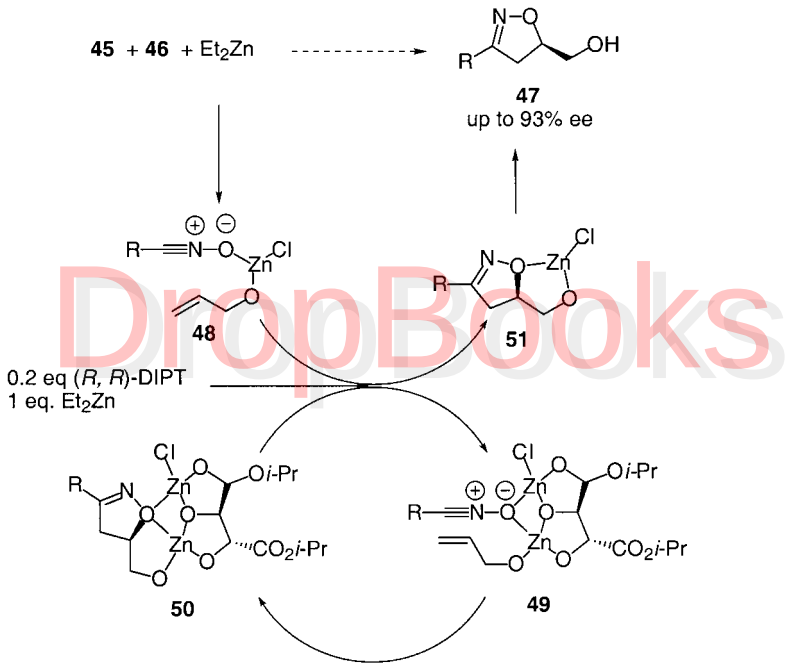
The first, and so far only, metal-catalyzed asymmetric 1,3-dipolar cycloaddition reaction of nitrile oxides with alkenes was reported by Ukaji et al. [76, 77]. Upon treatment of allyl alcohol **45** with diethylzinc and (*R*,*R*)-diisopropyltartrate, followed by the addition of diethylzinc and substituted hydroximoyl chlorides **46**, the isoxazolidines **47** are formed with impressive enantioselectivities of up to 96% ee (Scheme 6.33) [76].



Scheme 6.33

In an extension of this work they developed a catalytic version of the reaction in which the chiral ligand (*R*,*R*)-diisopropyltartrate (DIPT) was applied in 20 mol% [77]. In spite of the reduction of the amount of the chiral ligand similar high enantioselectivities of up to 93% ee were obtained in this work. The addition of a

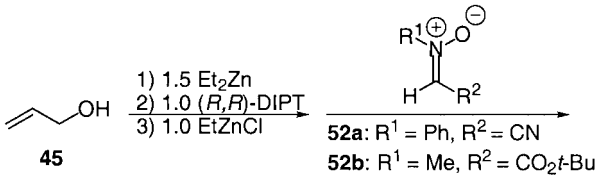
small amount of 1,4-dioxane proved to be crucial for the enantioselectivity of the reaction. A proposal for the reaction mechanism was given and it is outlined in Scheme 6.34. Allyl alcohol **45**, hydroximoyl chloride **46** and diethylzinc react to form **48**, which is mixed with the ligand and an additional amount of diethylzinc to form **49**. The achiral complex **48** is apparently much less activated for a 1,3-dipolar cycloaddition reaction compared to **49**, which controls the enantioselectivity of the reaction. The increased reactivity of **49** compared to **48** might be because of a ligand-accelerating effect of DIPT when coordinated to the metal. After formation of the isoxazoline **50**, the Zn-DIPT moiety of **50** proceeds in the catalytic cycle and **51** is formed. When the reaction is complete **51** is hydrolyzed to give **47** in up to 93% ee (R = *t*-Bu) [77].

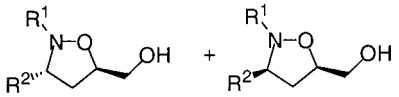


Scheme 6.34

The above described approach was extended to include the 1,3-dipolar cycloaddition reaction of nitrones with allyl alcohol (Scheme 6.35) [78]. The zinc catalyst which is used in a stoichiometric amount is generated from allyl alcohol **45**, Et_2Zn, (*R*,*R*)-diisopropyltartrate (DIPT) and EtZnCl. Addition of the nitrone **52a** leads to primarily *trans*-**53a** which is obtained in a moderate yield, however, with high ee of up to 95%. Application of **52b** as the nitrone in the reaction leads to higher yields of **53b** (47–68%), high *trans* selectivities and up to 93% ee. Compared to other metal-catalyzed asymmetric 1,3-dipolar cycloaddition reactions of

nitrones, this reaction cannot be assigned as normal or inverse electron-demand. The reaction is controlled, not primarily by the alteration of FMO energies, but by the chelation of the substrates to the catalyst leading to a favorable entropy of the pseudo-intramolecular intermediates.





trans-**53a**,**b**
up to 95% ee

cis-**53a**,**b**

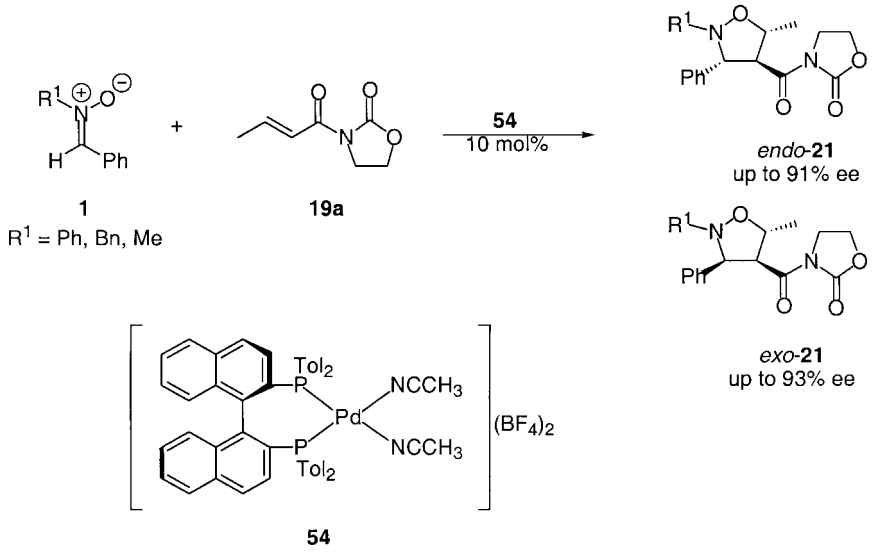
Scheme 6.35

It should also be mentioned that in connection with the investigations on MgX_2-BOX catalysts, Desimoni et al. also tested a $Zn(ClO_4)_2$-BOX catalyst for the 1,3-dipolar cycloaddition of a nitrone and acryloyloxazolidinone (see Scheme 6.17). Contrary to the magnesium catalysts, this zinc catalyst was *exo* selective as an 27:73 *exo*/*endo* ratio was observed, and 84% ee of the *exo* isomer was obtained [51].

6.10 Palladium Catalysts for Reactions of Nitrones

For the activation of a substrate such as **19a** via coordination of the two carbonyl oxygen atoms to the metal, one should expect that a hard Lewis acid would be more suitable, since the carbonyl oxygens are hard Lewis bases. Nevertheless, Furukawa et al. succeeded in applying the relative soft metal palladium as catalyst for the 1,3-dipolar cycloaddition reaction between **1** and **19a** (Scheme 6.36) [79, 80]. They applied the dicationic Pd-BINAP **54** as the catalyst, and whereas this type of catalytic reactions is often carried out at rt or at 0 °C, the reactions catalyzed by **54** required heating at 40 °C in order to proceed. In most cases mixtures of *endo*-**21** and *exo*-**21** were obtained, however, high enantioselectivity of up to 93% were obtained for reactions of some derivatives of **1**.

A transition structure model was proposed which accounts for the high selectivities obtained for some of the substrates [80]. In the structure shown in Scheme 6.37 the two phosphorus atoms of the Tol-BINAP ligand and the two car-



Scheme 6.36

bonyl oxygens of the crotonoyl oxazolidinone are arranged in a square planar fashion around the palladium center (note that the counter-ions are omitted from this model). From the model the upper *si* face of the alkene is sterically available for the cycloaddition reaction, while the *re* face is shielded by one of the Tol-BINAP *p*-tolyl groups.

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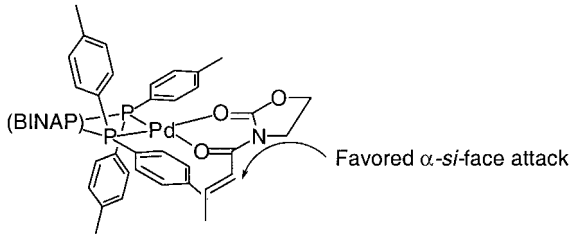


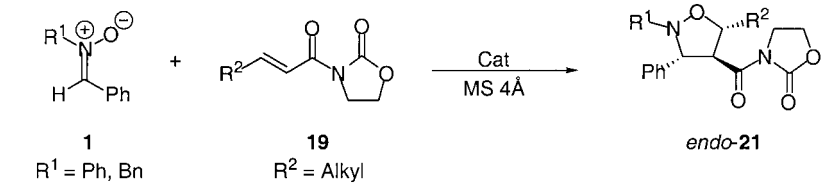
Scheme 6.37

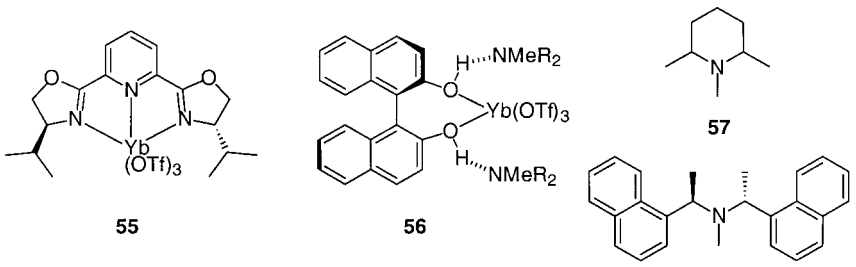
Furukawa et al. also applied the above described palladium catalyst to the inverse electron-demand 1,3-dipolar cycloaddition of nitrones with vinyl ethers. However, all products obtained in this manner were racemic [81].

6.11
Lanthanide Catalysts for Reactions of Nitrones

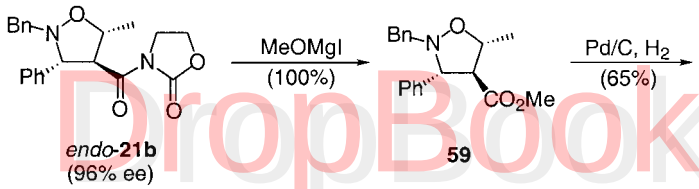
In 1997 the application of two different chiral ytterbium catalysts, **55** and **56** for the 1,3-dipolar cycloaddition reaction was reported almost simultaneously by two independent research groups [82, 83]. In both works it was observed that the achiral $Yb(OTf)_3$ and $Sc(OTf)_3$ salts catalyze the 1,3-dipolar cycloaddition between nitrones **1** and alkenoyloxazolidinones **19** with *endo* selectivity. In the first study 20 mol% of the $Yb(OTf)_2$-pyridine-bisoxazoline complex **55** was applied as the catalyst for reactions of a number of derivatives of **1** and **19**. The reactions led to *endo*-selective 1,3-dipolar cycloadditions giving products with enantioselectivities of up to 73% ee (Scheme 6.38) [82]. In the other report Kobayashi et al. described a 1,3-dipolar cycloaddition catalyzed by 20 mol% of the $Yb(OTf)_3$–BINOL complex **56** in the presence of the achiral tertiary amine **57** [83]. In this approach the nitrone **1** was formed in situ from the respective aldehyde and hydroxylamine. High *endo* selectivities were observed and for one derivative the product *endo*-**21** (R^1 = Bn, R^2 = Me) was obtained with 78% ee [83]. In an extension of these investigations the 1,3-dipolar cycloaddition reaction was performed in the presence of 20 mol% of the catalyst **56** and 40 mol% of a the chiral amine **58** [84]. By substituting the achiral amine **57** with the complex chiral amine **58** the selectivity of the reaction was largely improved. For the reactions of some derivatives of **1** and **19**, *endo*-**21** was obtained as a single diastereomer and enantioselectivities of up to 96% ee were achieved. Further investigation in this field by Kobayashi et al. led to the finding that the absolute stereoselectivity of the reaction was reversed when the reaction was performed in the absence of MS 4 Å [85]. This observation makes an analog to the MgX_2-BOX-catalyzed reactions, where a similar incidence was observed [49]. In the reaction catalyzed by **56** using **58** as the additive *endo*-**21** (R^1 = Bn, R^2 = Me) was obtained in 96% ee in the presence of MS 4 Å. In the absence of MS 4 Å the opposite enantiomer was obtained in 50% ee. This inverse selectivity could be improved by using various *N*-oxides as a third additive [85].

Whereas there are numerous examples of the application of the products from diastereoselective 1,3-dipolar cycloaddition reaction in synthesis [7, 8], there are only very few examples on the application of the products from metal-catalyzed asymmetric 1,3-dipolar cycloaddition reaction in the synthesis of potential target molecules. The reason for this may be due to the fact that most metal-catalyzed asymmetric 1,3-dipolar cycloaddition reaction have been carried out on model systems that have not been optimized for further derivatization. One exception of this is the synthesis of a *β*-lactam by Kobayashi and Kawamura [84]. The isoxazolidine *endo*-**21b**, which was obtained in 96% ee from the $Yb(OTf)_3$-BINOL-catalyzed 1,3-dipolar cycloaddition reaction, was converted into the ester derivative **59**, quantitatively. Hydrogenation over palladium on carbon opens the isoxazolidine ring and cleaves the *N*-benzyl moiety to give **60**. Following silyl protection of the hydroxy group in **60**, the final ring-closure is mediated by LDA to give the *β*-lactam **62** in a high yield with a conserved optical purity of 96% ee (Scheme 6.39).





Scheme 6.38



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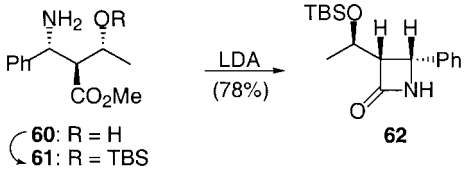


Scheme 6.39

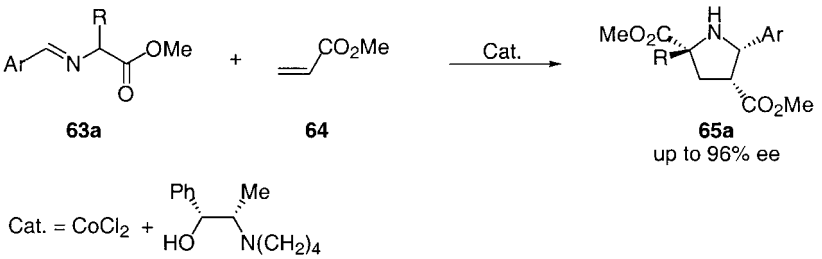
6.12
Cobalt, Manganese, and Silver Catalysts for Reactions of Azomethine Ylides

The first report on metal-catalyzed asymmetric azomethine ylide cycloaddition reactions appeared some years before this topic was described for other 1,3-dipolar cycloaddition reactions [86]. However, since then the activity in this area has been very limited in spite of the fact that azomethine ylides are often stabilized by metal salts as shown in Scheme 6.40.

Grigg et al. have found that chiral cobalt and manganese complexes are capable of inducing enantioselectivity in 1,3-dipolar cycloaddition reactions of azomethine

Scheme 6.40

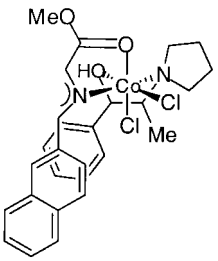
ylides derived from arylidene imines of glycine (Scheme 6.41) [86]. This work was published in 1991 and is the first example of a metal-catalyzed asymmetric 1,3-dipolar cycloaddition. The reaction of azomethine ylide **63a** with methyl acrylate **64** required a stoichiometric amount of cobalt and two equivalents of the chiral ephedrine ligand, however, up to 96% ee was obtained for the 1,3-dipolar cycloaddition product **65a.**



63a **64** **65a**
up to 96% ee

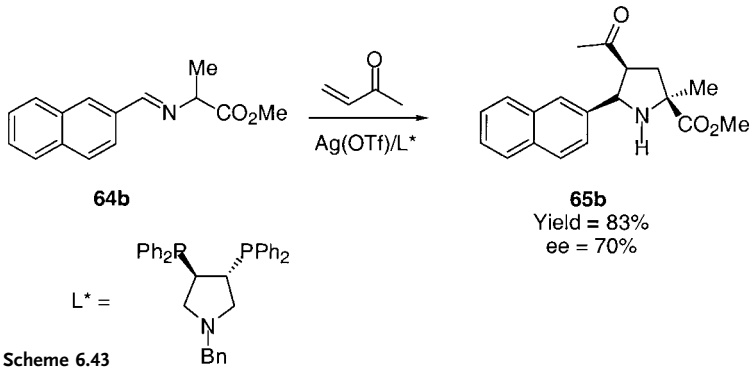
Scheme 6.41

The yields of **65a** were in the range of 45–84% and the highest ee were obtained when Ar = 2-naphthyl, 4-BrC_6H_4 or 4-$MeOC_6H_4$, and when methyl acrylate was used as the solvent. Both the reaction time and ee are dependent on the counterion, as the use of CoF_2 as the catalyst leads to a very slow 1,3-dipolar cycloaddition reaction with low chiral induction compared to the use of $CoCl_2$. A proposed working model for the asymmetric induction is shown in Scheme 6.42. The *cis* arrangement of the methyl and phenyl group of the ligand in **66** results in a pseudo equatorial conformation of the phenyl group and provides an effective blockade of one face of the dipole [86].



Scheme 6.42 **66**

In a more recent publication the same group mentions that Ag(I) salts in combination with chiral phosphine ligands can catalyze the 1,3-dipolar cycloaddition involving the azomethine precursor **64b** and methyl vinyl ketone (Scheme 6.43) [87]. The reaction, which presumably also required a stoichiometric amount of the catalyst, proceeds to give **65b** in a good yield with 70% ee.



Scheme 6.43

6.13 Rhodium Catalysts for Reactions of Carbonyl Ylides

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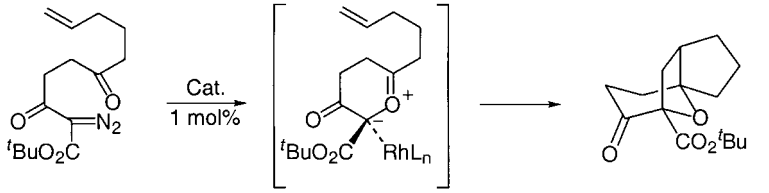
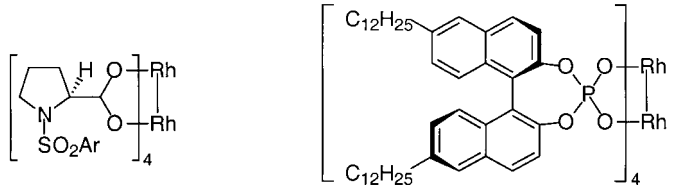
The development in the area of rhodium carbenes that are formed from diazo compounds, has led to the present access to carbonyl ylides [14, 15]. In the first metal-catalyzed asymmetric version of this reaction from 1997 Hodgson et al. [88] investigated the intramolecular 1,3-dipolar cycloaddition reaction of the carbonyl ylide precursor **67** (Scheme 6.42). In the presence of 1 mol% of the catalyst **70** in a hydrocarbon solvent, the reaction proceeded to give **69** in 93% yield and with 52% ee. The exact nature of the interaction between the rhodium catalyst and the carbonyl ylide in the intermediate **68** is unknown. However, the presence of the catalyst/ligand-induced control of enantioselectivity [88, 89] and of the regioselectivity in earlier work [90, 91], strongly indicate that the catalyst is in some manner associated with the 1,3-dipole in the cycloaddition step. In a more recent work the same authors tested a number of dirhodium tetrakis(1,1′-binaphthyl-2,2′-diyl phosphonate) catalysts for the reaction [89]. The best results were obtained with the catalyst **71** that had been developed for this reaction. The advantage of this ligand is that it has a high solubility in hexane, which is the solvent of choice for this reaction. By the application of 1 mol% of catalyst **71** up to 90% ee of the tricyclic product **69** was obtained.

The intermolecular version of the above described reaction has also been reported [92]. In the first example the reaction of a rhodium catalyst carbonyl ylide with maleimide was studied. However, only low enantioselectivities of up to 20% ee were obtained [92]. In a more recent report Hashimoto et al. were able to induce high enantioselectivities in the intermolecular carbonyl ylide reaction of the



67 68 69

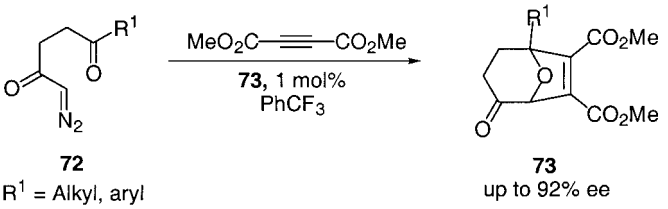
Cat. **70**: ee = 52%
Cat. **71**: ee = 90%



70 71

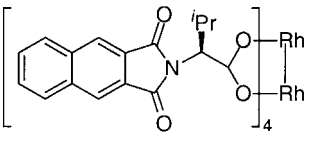
Scheme 6.44

precursor **72** with dimethyl acetylenedicarboxylate [93]. After optimizing the reaction conditions and testing a series of catalyst, they were able to obtain a series of products **73** in the reaction catalyzed by 1 mol% of **74** in moderate to good yields with enantioselectivities ranging from 80 to 92% ee (Scheme 6.45). It was important for both yield and enantioselectivity that the reaction was carried out in trifluoromethylbenzene as the solvent. They also showed that the reaction could be performed with substrates giving the corresponding bicyclo[2,2,1] and bicyclo[4,2,1] products with 68% and 80% ee, respectively.



72
R^1 = Alkyl, aryl

73
up to 92% ee



Scheme 6.45 **74**

6.14 Conclusion

The reactions of nitrones constitute the absolute majority of metal-catalyzed asymmetric 1,3-dipolar cycloaddition reactions. Boron, aluminum, titanium, copper and palladium catalysts have been tested for the inverse electron-demand 1,3-dipolar cycloaddition reaction of nitrones with electron-rich alkenes. Fair enantioselectivities of up to 79% ee were obtained with oxazaborolidinone catalysts. However, the AlMe-3,3′-Ar-BINOL complexes proved to be superior for reactions of both acyclic and cyclic nitrones and more than >99% ee was obtained in some reactions. The $Cu(OTf)_2$-BOX catalyst was efficient for reactions of the glyoxylate-derived nitrones with vinyl ethers and enantioselectivities of up to 93% ee were obtained.

For the normal electron-demand 1,3-dipolar cycloaddition reaction of nitrones with electron-deficient alkenes a number of metal complexes have been applied. All of these have in common that they favor a bidentate coordination of the alkenoyloxazolidinone (or succinimide) to the metal catalyst. Most of these reactions proceeded with *endo* selectivity. The MgX_2-BOX complexes induced ee in the nineteen-eighties in the best cases and depending on the counter-ion and the absence and presence of MS, the absolute induction could be reversed. In a few cases high enantioselectivities were obtained using $Pd(BF_4)_2$-BINAP complexes, however, this catalyst suffered from a lack of *endo*/*exo* selectivity. The $Ti(OTs)_2$-TADDOLate catalyst induced very high *endo* selectivity and up to 93% ee was obtained, however, a large catalyst loading of 50% had to be applied in these reactions. Even higher selectivities of up to 96% ee were obtained when the $Yb(OTf)_3$-BINOL-chiral amine complexes were used as the catalyst, but also in this case a high loading of 60% of chiral material had to be applied. The chiral $Ni(ClO_4)_2$-DBFOX/Ph has been the most selective catalyst for the *endo*-selective normal electron-demand 1,3-dipolar cycloaddition reaction so far. Application of 1–10 mol% of this catalyst induced in general very high enantioselectivities of up to 99% ee.

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It has been more difficult to obtain the *exo* isomer in the above described reaction. Application of the $TiCl_2$-TADDOLate complex induced fair *exo* selectivity and up to 60% ee. This was improved by the application of succinimide as an auxiliary for the alkene. This approach has been the only entry to a highly *exo* selective reaction and up to 72% ee of the *exo* isomer was obtained. In the $Pd(BF_4)_2$–BINAP-catalyzed reaction which gave mixtures of the *endo* and *exo* isomers, high ee of up to 93% was in a single case obtained for the minor *exo* isomer. In one case it was also observed that a $Zn(OTf)_2$-BOX complex induced some *exo* selectivity and up to 82% ee of the *exo* isomer.

Zinc-tartrate complexes were applied for reactions of both nitrones and nitrile oxides with allyl alcohol and for both reaction types selectivities of more than 90% ee were obtained. Whereas the reactions of nitrones required a stoichiometric amount of the catalyst the nitrile oxide reactions could be performed in the presence of 20 mol% of the catalyst. This is the only example on a metal-catalyzed asymmetric 1,3-dipolar cycloaddition of nitrile oxides. It should however be no-

ticed that very recently a highly enantioselective antibody-catalyzed 1,3-dipolar cycloaddition reaction of a nitrile oxide was reported [94].

Although the first metal-catalyzed asymmetric 1,3-dipolar cycloaddition reaction involved azomethine ylides, there has not been any significant activity in this area since then. The reactions that were described implied one of more equivalents of the chiral catalyst, and further development into a catalytic version has not been reported.

The rhodium-catalyzed tandem carbonyl ylide formation/1,3-dipolar cycloaddition is an exciting new area that has evolved during the past 3 years and high selectivities of >90% ee was obtained for both intra- and intermolecular reactions with low loadings of the chiral catalyst.

The development of metal-catalyzed asymmetric 1,3-dipolar cycloaddition reactions is probably going to continue during the next decade. High level of control of the reactions of nitrones has been obtained, and for these reactions one of the next challenges is to explore new substrates that are designed for application in synthesis. The development of metal-catalyzed asymmetric reactions of the other 1,3-dipoles that have been mentioned in this chapter is still in the initial phase. The development has not even taken its beginning for a series of other important 1,3-dipoles such as azomethine imines, azides and nitrile imines. Thus, there are several challenges and new possibilities in this area and it is going to be very exciting to follow the future developments.

Acknowledgment

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7
Aqua Complex Lewis Acid Catalysts for Asymmetric 3+2 Cycloaddition Reactions

Shuji Kanemasa

7.1
Introduction

Because of the pioneering work and outstanding contributions of Huisgen and coworkers [1], 1,3-dipolar cycloaddition reactions are now well known and widely recognized as the most useful access to heterocyclic compounds. Especially, the high stereospecificity of 1,3-dipolar cycloaddition reactions to alkene dipolarophiles makes this reaction one of the most reliable and useful synthetic methodologies for the short-step construction of stereochemically defined heterocycles [2]. A wide variety of complex functional groups are masked in the heterocycles prepared by stereoselective 1,3-dipolar cycloaddition reactions, and simple unmasking transformations of these heterocycles lead to useful functionalized building blocks [3].

The author has been involved for quite a long time in the study of Lewis acid catalysis of 1,3-dipolar cycloaddition reactions. From his research group, a series of methodologies directed to the Lewis acid-mediated stereochemical and regiochemical control of 1,3-dipolar cycloaddition reactions has been reported; this includes:

(i) the chemistry of *N*-metalated azomethine ylides [4–7];
(ii) the chemistry of Lewis acid-induced stereo- and regiocontrol of nitrone cycloaddition reactions to electron-deficient alkenes [8];
(iii) the chemistry of magnesium ion-mediated stereo- and regiocontrol of nitrile oxide cycloaddition reactions to allylic alcohols [9]; and
(iv) the chemistry of magnesium- and other metal ion-mediated stereo- and regiocontrol of nitrone cycloaddition reactions to allylic alcohols [10].

It is only quite recent that a new wave of enantioselective version of Lewis acid-catalyzed 1,3-dipolar cycloadditions has appeared in the literature after many reports accumulated from some pioneering groups in related fields [11–17]. These works have attracted mush attention from synthetic organic chemists. Pioneers in each field include Grigg (azomethine ylide) [18], Ukaji (nitrile oxide and nitrone) [19–21], Jørgensen (nitrone) [22–30], Scheeren (nitrone) [31], Kobayashi (nitrone) [32, 33], Furukawa (nitrone) [34], and Hashimoto (carbonyl ylide) [35]. It was delight that the author also became a member of this pioneering group with his first report on the development of a new tridentate *trans*-chelating chiral ligand

[36–38], (*R,R*)-4,6-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline), hereafter designated *R,R*-DBFOX/Ph. A variety of transition metal and some other metal perchlorates make stable complexes with this ligand. The aqua complexes of *R,R*-DBFOX/Ph have high catalytic activity as Lewis acids, and can be stored in the open air without loss of catalytic activity [39]. Because of their high tolerance to a variety of coordinating nucleophiles, it was thought they could be successfully utilized in asymmetric 1,3-dipolar cycloaddition reactions.

In this chapter the aqua complex Lewis acid catalysts [40–42] prepared from *R,R*-DBFOX/Ph ligand are reviewed. In the following sections their synthesis, complexation, the nature of the complexes, catalytic activity, chiral amplification, and applications to Diels-Alder reactions, nitrone cycloadditions, nitronate cycloadditions, and diazoalkane cycloadditions will be presented. The most attractive feature of *R,R*-DBFOX/Ph complex catalysts is their high tolerance to coordinating nucleophiles so that they can be used in Lewis acid-catalyzed asymmetric reactions employing strong nucleophiles. The author would, therefore, like to add one section about *R,R*-DBFOX/Ph complex-catalyzed asymmetric conjugate addition reactions using thiols, hydroxylamines, and carbon nucleophiles/amine bases.

7.2 DBFOX/Ph-Transition Metal Complexes and Diels-Alder Reactions

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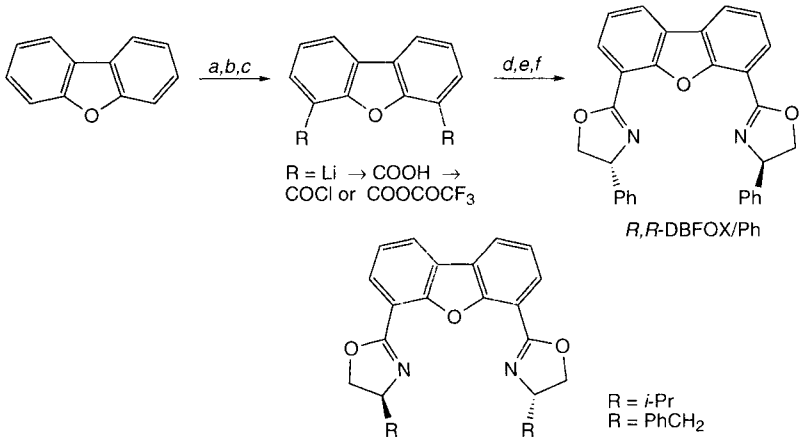
The cationic aqua complexes prepared from *trans*-chelating tridentate ligand, *R,R*-DBFOX/Ph, and various transition metal(II) perchlorates induce absolute enantioselectivity in the Diels-Alder reactions of cyclopentadiene with 3-alkenoyl-2-oxazolidinone dienophiles. Unlike other bisoxazoline type complex catalysts [38, 43–54], the *R,R*-DBFOX/Ph complex of $Ni(ClO_4)_2 \cdot 6H_2O$, which has an octahedral structure with three aqua ligands, is isolable and can be stored in air for months without loss of catalytic activity. Iron(II), cobalt(II), copper(II), and zinc(II) complexes are similarly active.

7.2.1 Preparation and Structure of the Catalysts

Synthesis of the *R,R*-DBFOX/Ph ligand starts with the known bislithiation at the 4,6-positions of the commercially available dibenzofuran (Scheme 7.1) [39]. The lithiated intermediate [55] was dicarboxylated with gaseous carbon dioxide [56] to give 4,6-dibenzofurandicarboxylic acid which was treated under reflux with thionyl chloride in the presence of trifluoroacetic acid. Removal of the excess thionyl chloride was followed by treatment with (*R*)-2-phenyl-2-aminoethanol to give the corresponding amide. The usual cyclization procedure including a sequence of chlorination of the hydroxyl group to chloroethyl moiety and cyclization by with the aid of sodium hydroxide gave *R,R*-DBFOX/Ph. Other ligands having isopropyl (*S,S*-DBFOX/*i*-Pr) and benzyl (*S,S*-DBFOX/Bn) shielding substituents at the 4-position of the oxazoline ring can be prepared by similar routes.



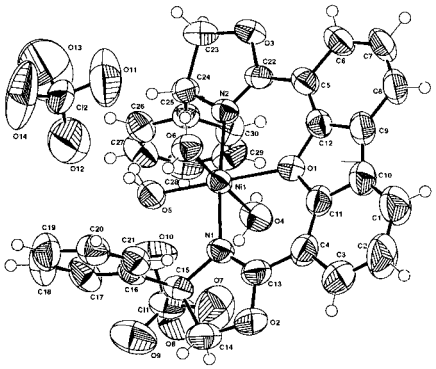
a: *n*-BuLi in THF at -40 °C → rt → reflux, *b:* Gaseous CO_2 and acidified (44%), *c:* $SOCl_2$ in CF_3COOH, reflux for 3 h, then excess $SOCl_2$ removed, *d:* (*R*)-Phenylglycinol/Et_3N in $CHCl_3$ at rt for 24 h, *e:* $SOCl_2$ at rt for 3 h, *f:* Aqueous NaOH in MeOH/$CHCl_3$ at rt for 24 h (63% based on the dicarboxylic acid).

Scheme 7.1

The complexation procedure included addition of an equimolar amount of *R,R*-DBFOX/Ph to a suspension of a metal salt in dichloromethane. A clear solution resulted after stirring for a few hours at room temperature, indicating that formation of the complex was complete. The resulting solution containing the catalyst complex was used to promote asymmetric Diels-Alder reactions between cyclopentadiene and 3-acryloyl-2-oxazolidinone. Both the catalytic activity of the catalysts and levels of chirality induction were evaluated on the basis of the enantioselectivities observed for the *endo* cycloadduct.

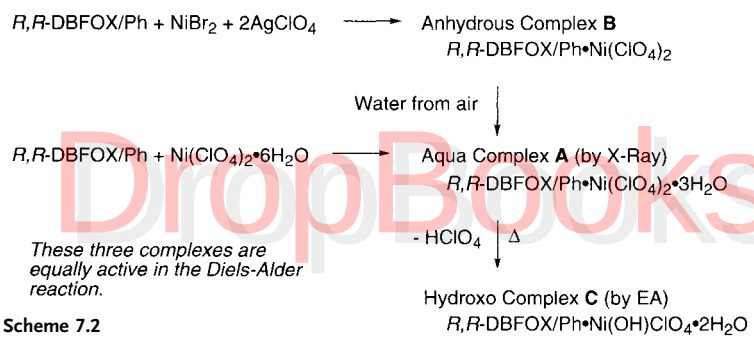
The anhydrous complex *R,R*-DBFOX/Ph·$Ni(ClO_4)_2$ was prepared from *R,R*-DBFOX/Ph and $NiBr_2$ followed by treatment with two equimolar amounts of $AgClO_4$. When this complex was crystallized from acetone-dichloromethane, some molecules of water were incorporated to give fine crystals of the complex. On the basis of the X-ray stereostructure, the complex had a molecular formula *R,R*-DBFOX/Ph·$Ni(ClO_4)_2 \cdot 3H_2O$ with an octahedral structure **A** (Scheme 7.2). The two oxazoline rings are coplanar with the plane of dibenzofuran, and the nickel ion is bound to three water molecules and the furan oxygen atom. The N–Ni–N bond is almost linear ($\measuredangle$ N–Ni–N = 174.2°), indicating that *R,R*-DBFOX/Ph is *trans*-chelating toward Ni(II) ion. The two N–Ni distances are 2.059 and 2.065 Å which are typical of bond distances between an imine nitrogen and a nickel ion. The aqua complex **A** which was directly prepared from *R,R*-DBFOX/Ph ligand and $Ni(ClO_4)_2 \cdot 6H_2O$ had high catalytic activity and enantioselectivity in the Diels-Alder reaction (–40 °C, quant, *endo*/*exo* = 97:3, >99% ee), and the activity remained even after storage in air at room temperature for months. Drying of the aqua complex **A** under vacuum and heating led to a new complex **C** which has a hydroxo monoperchlorate complex structure on the basis of elemental analysis. Hy-

droxo monoperchlorate complex **C** also has strong catalytic activity in the Diels-Alder reaction and gives the absolute enantioselectivity (–40 °C, 99%, *endo*/*exo* = 97 : 3, > 99% ee).



Complex **A**

N(1)-Ni(1)	2.059 Å
N(2)-Ni(1)	2.065
Ni(1)-O(5)	2.028
Ni(1)-O(6)	2.049
Ni(1)-O(4)	2.057
Ni(1)-O(1)	2.123
N(1)-Ni(1)-N(2)	174.3°
O(1)-Ni(1)-O(4)	88.1°
N(1)-Ni(1)-O(1)	87.3°
O(1)-Ni(1)-O(5)	179.1°



Scheme 7.2

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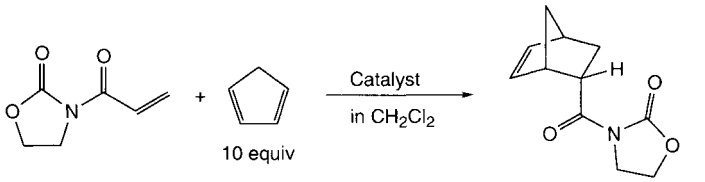
7.2.2 Diels-Alder Reactions

Commercially available nickel(II) perchlorate hexahydrate, $Ni(ClO_4)_2 \cdot 6H_2O$, is totally insoluble in dichloromethane but dissolves in the presence of *R*,*R*-DBFOX/Ph ligand. The resulting bluish green complex **A** has high catalytic activity. Diels-Alder reactions between cyclopentadiene and 3-acryloyl-2-oxazolidinone with 10 mol% of the aqua complex at –40 °C give a single enantiomer of the *endo* cycloadduct (Scheme 7.3). Both the chemical yield and the *endo*/*exo* ratio are also excellent (96% yield, *endo*/*exo* = 97 : 3). High enantioselectivity remains with a catalytic loading of 2 mol% of the nickel complex (96% ee). With a small catalytic loading, however, the reaction rate is too low to neglect an undesired effect from the uncatalyzed reaction.

With β-substituted dienophiles, which are much less reactive than the unsubstituted compounds, reactions were performed at room temperature (Scheme 7.4). The observed enantioselectivities of 93% and 94% ee, for dienophiles with a pri-



Catalyst = *R,R*-DBFOX/Ph•$Ni(ClO_4)_2$•$3H_2O$ and *exo*-cycloadduct

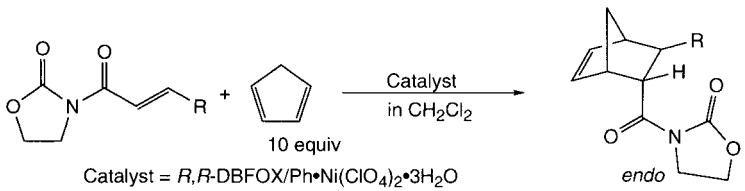
Cat/mol%	Temp/°C	Time/h	Yield/%	*endo/exo*	% ee
10	rt	2	95	92/8	89
10	-20	24	97	97/3	95
10	-40	14	96	97/3	>99
10	-78	96	quant	98/2	>99
2	-40	21	95	98/2	96
2	0	4	96	95/5	89
1	rt	1	95	92/8	78

Equimolar amounts of *R,R*-DBFOX/Ph and $Ni(ClO_4)_2$•$6H_2O$ are stirred in dichloromethane for a few hours at room temperature to give a clear green solution.

Scheme 7.3

mary alkyl substituent, are satisfactory enough for the conditions employed. The phenyl-substituted substrate, however, resulted in a rather low chemical yield with poor enantioselectivity even when the reaction was catalyzed by the anhydrous complex **B** prepared in-situ from *R,R*-DBFOX/Ph, $NiBr_2$ and $AgSbF_6$. Use of the aqua complex was less effective (rt, 72 h, 20%, 51% ee for the *endo* cycloadduct).

The nickel and cobalt aqua complexes were even more effective, both for catalytic activity and enantioselectivity, than the corresponding anhydrous complexes (Scheme 7.5). Addition of three equivalents of water to the anhydrous nickel complex recovered the catalytic efficiency. DBFOX/Ph complexes derived from manganese(II), iron(II), copper(II), and zinc(II) perchlorates, both anhydrous and "wet",



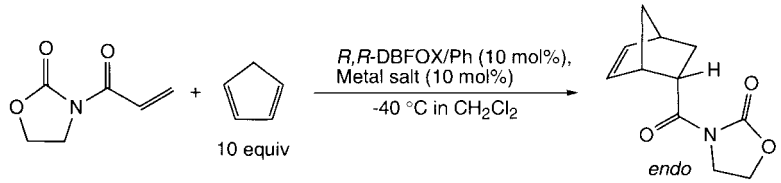
Catalyst = *R,R*-DBFOX/Ph•$Ni(ClO_4)_2$•$3H_2O$

R	Cat/mol%	Temp/°C	Time/h	Yield/%	*endo/exo*	% ee
H[a]	10	-40	72	98	98/2	>99
H[b]	10	-40	72	quant	97/3	>99
H[c]	10	-40	48	quant	96/4	>99
H[d]	10	-40	72	97	88/12	-52
Me	10	rt	20	90	92/8	93
n-Pr	10	rt	72	quant	93/7	94
Ph[e]	10	rt	48	54	nd	74

[a]Single crystals of 1:1 complex. [b]1:1 Catalyst obtained by evaporation of CH_2Cl_2. [c]After 3 months in an open air. [d]Ligand: (*R,R*)-isopropylidene-2,2'-bis(4-phenyloxazoline). [e]Anhydrous complex catalyst prepared from $NiBr_2$ and $AgSbF_6$.

Scheme 7.4

had high catalytic activity resulting in excellent enantioselectivity in the Diels-Alder reactions, where the "wet" catalysts were prepared by addition of three equivalents of water to the anhydrous catalysts. On the other hand, the DBFOX/Ph complexes of Fe(III), Cu(I), Rh(III), Pd(II), Ag(I), Sn(II) salts and some lanthanides were much less effective. When the results observed in the Diels-Alder reactions using anhydrous and aqua complexes are compared, it is clear that the aqua complexes are again usually more fruitful. One exception was the iron(III) complex, which provided improved enantioselectivity when the catalyst was prepared in the presence of 3-acryloyl-2-oxazolidinone and 4-Å molecular sieve (MS 4).



Metal Salts	*endo*/*exo*	Yield/%	ee %	Metal Salts	*endo*/*exo*	Yield/%	ee %
$Mg(ClO_4)_2$	97/3	quant	91(>99)[a]	$Mg(ClO_4)_2+3H_2O$	96/4	68	48
$MnBr_2+2AgClO_4$	95/5	95	79	$Mn(ClO_4)_2{\cdot}6H_2O$	97/3	91	83
$FeCl_2+2AgClO_4$	99/1	90	98	$Fe(ClO_4)_2+3H_2O$	98/2	92	97
$CoBr_2+2AgClO_4$	97/3	quant	93	$Co(ClO_4)_2{\cdot}6H_2O$	97/3	97	99
$NiBr_2+2AgClO_4$	95/5	quant	96	$Ni(ClO_4)_2{\cdot}6H_2O$	97/3	96	>99
$CuCl_2+2AgClO_4$	96/4	97	92	$Cu(ClO_4)_2{\cdot}6H_2O$	98/2	95	95
$ZnI_2+2AgClO_4$	98/2	99	97	$Zn(ClO_4)_2{\cdot}6H_2O$	98/2	97	97
	Anhydrous complex				Aqua complex		

[a]One equiv of DBFOX/$Mg(ClO_4)_2$ was used.

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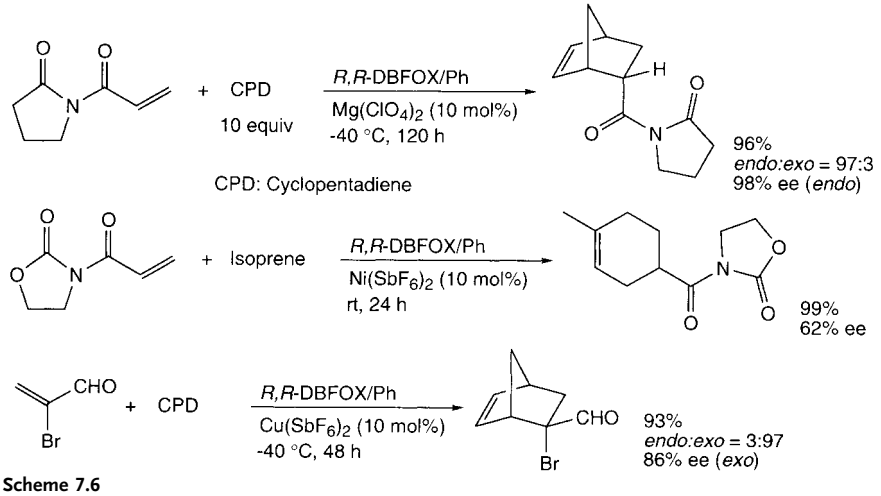
Scheme 7.5

Diels-Alder reactions of other substrates were catalyzed by the metal complexes of *R,R*-DBFOX/Ph ligand (Scheme 7.6, catalysts: always 10 mol%). Dienophiles such as *N*-acryloyl-2-pyrrolidinone and methyl (*E*)-2-oxo-4-phenyl-3-butenoate were similarly activated with the magnesium complex to give the corresponding cycloadducts, the former reaction giving an excellent enantioselectivity. Isoprene, as sluggish acyclic diene, reacted with 3-acryloyl-2-oxazolidinone in the presence of the anhydrous nickel catalyst, but the selectivity was not satisfactory. Although 1-methoxy-1,3-butadiene and 1-trimethylsilyloxy-1,3-butadiene were expected in general to be more reactive dienes than cyclopentadiene, this expectation was not upheld in the reactions catalyzed by *R,R*-DBFOX/Ph complexes. The oxygen substituents at 1-position of these dienes would be sterically hindered by the plane of dibendofuran ring in the transition state. The monodentate dienophile 2-bromoacrolein had high enantioselectivity in the reaction with cyclopentadiene when catalyzed by the copper(II) complex.

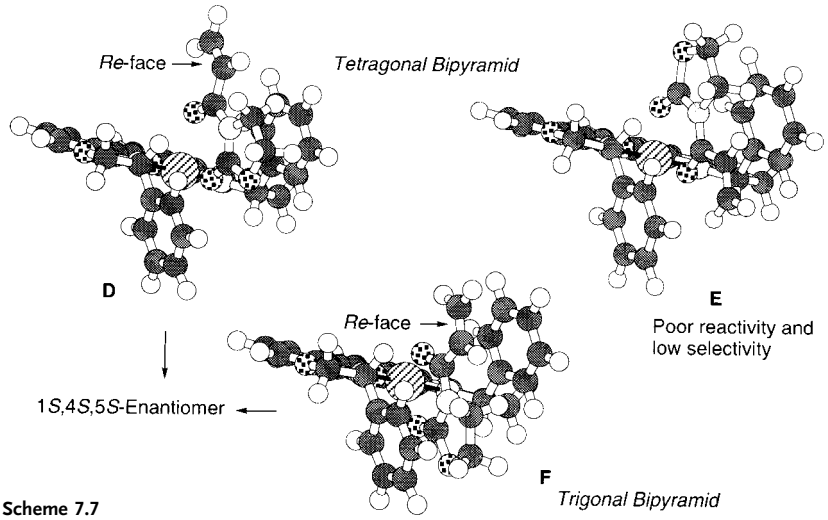


Scheme 7.6

7.2.3
Structure of the Substrate Complexes

On the basis of the absolute configuration of the *endo* cycloadduct which was assigned as (1*S*,2*S*,4*S*)-3′-(bicyclo[2.2.1]hept-5-en-2-yl)-2′-oxazolidinone, we propose that the reacting catalyst-substrate (dienophile) complex between *R,R*-DBFOX/Ph·$Ni(ClO_4)_2 \cdot 3H_2O$ and 3-acryloyl-2-oxazolidinone is a square bipyramidal structure containing an octahedral nickel ion. Although there is evidence for the existence of two coordination structures, **D** and **E** in solution as mentioned below, the sterically more hindered or π-stacking **E** should be less reactive than **D** (Scheme 7.7). Therefore, the complex **D** is responsible for the highly selective reaction on the *re* face with respect to the α-carbon of dienophile. Coordination structures such as **D** and **E** are the only possible substrate complexes. This structural simplicity is an important advantage of *R,R*-DBFOX complexes over the traditional *cis*-chelating bisoxazoline ligands, where a number of possible substrate complexes make it difficult to analyze the transition state structure.

In the substrate complexes, e.g. **D** and **E** shown in Scheme 7.7, three kinds of ligand are coordinating on to the nickel ion: *R,R*-DBFOX/Ph (Ln*), the chelating dienophile (ACC), and water. The first two should compete each other, and this competition poses a general and serious problem in the reactions catalyzed by complexes of neutral chiral ligands. If the substrate ACC is a better ligand than the chiral ligand Ln*, then effective catalysis is not expected. The results suggest that the chiral ligand Ln* is a much better ligand than the dienophile ACC in this case. Formation of the tight complex *R,R*-DBFOX/Ph·$Ni(ClO_4)_2 \cdot$Ln is one of the most attractive features of the tridentate *R,R*-DBFOX/Ph ligand (Scheme 7.8). The nitrogen-nitrogen distance of 4.1 Å ensures the high stability of nickel complex. As mentioned above, the solubility of $Ni(ClO_4)_2 \cdot 6H_2O$ in dichloromethane is very low in the absence of *R,R*-



Scheme 7.7

DBFOX/Ph ligand, and the dienophile itself does not solubilize the nickel ion at all. No rate acceleration is observed in the $Ni(ClO_4)_2 \cdot 6H_2O$-catalyzed Diels-Alder reaction in the absence of *R,R*-DBFOX/Ph. Accordingly, excess amounts of $Ni(ClO_4)_2 \cdot 6H_2O$ can be employed in the reaction without loss of enantioselectivity, the amount of nickel ion necessary for the 1:1 complexation is extracted by *R,R*-DBFOX/Ph ligand into solution. Such improved solubility is again no doubt due to the exceptionally high stability of *R,R*-DBFOX/Ph·Ni(II) complex.

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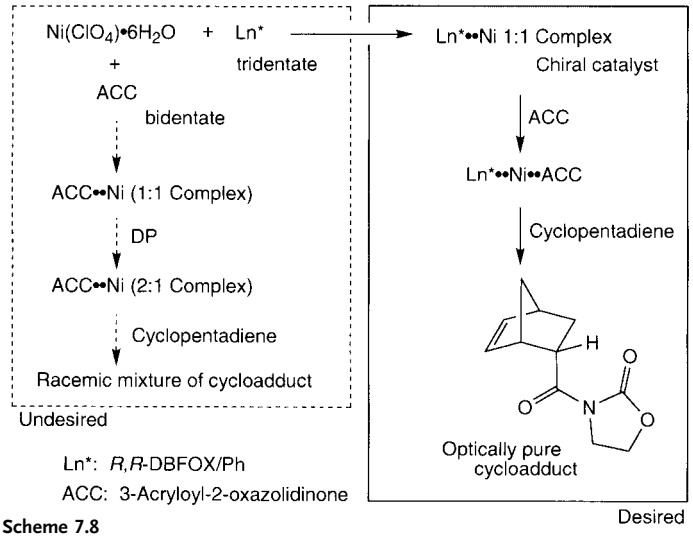
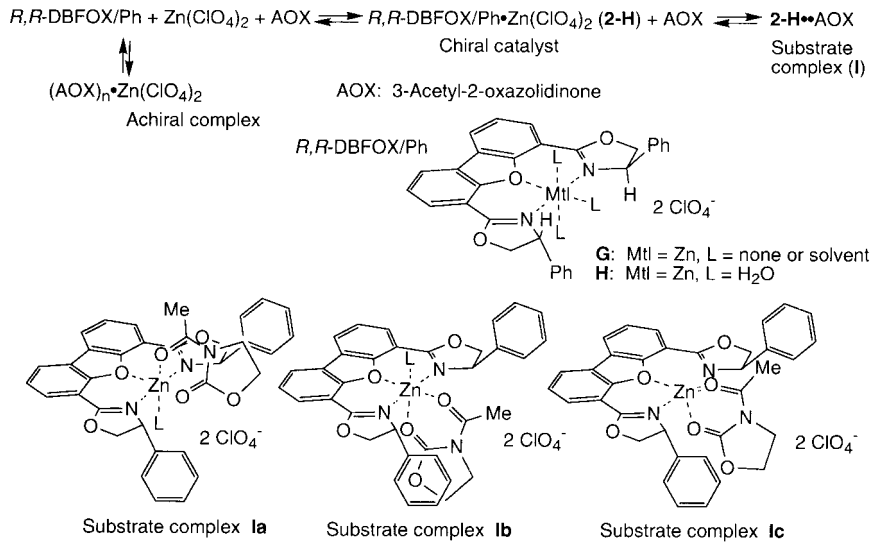


Scheme 7.8

Although the aqua nickel(II) complex **A** was confirmed to be the active catalyst in the Diels-Alder reaction, no information was available about the structure of complex catalyst in solution because of the paramagnetic character of the nickel(II) ion. Either isolation or characterization of the substrate complex, formed by the further complexation of 3-acryloyl-2-oxazolidinone on to the *R,R*-DBFOX/Ph·$Ni(ClO_4)_2$ complex catalyst, was unsuccessful. One possible solution to this problem could be the NMR study by use of the *R,R*-DBFOX/Ph-zinc(II) complex (**G** and **H**, Scheme 7.9) [57].

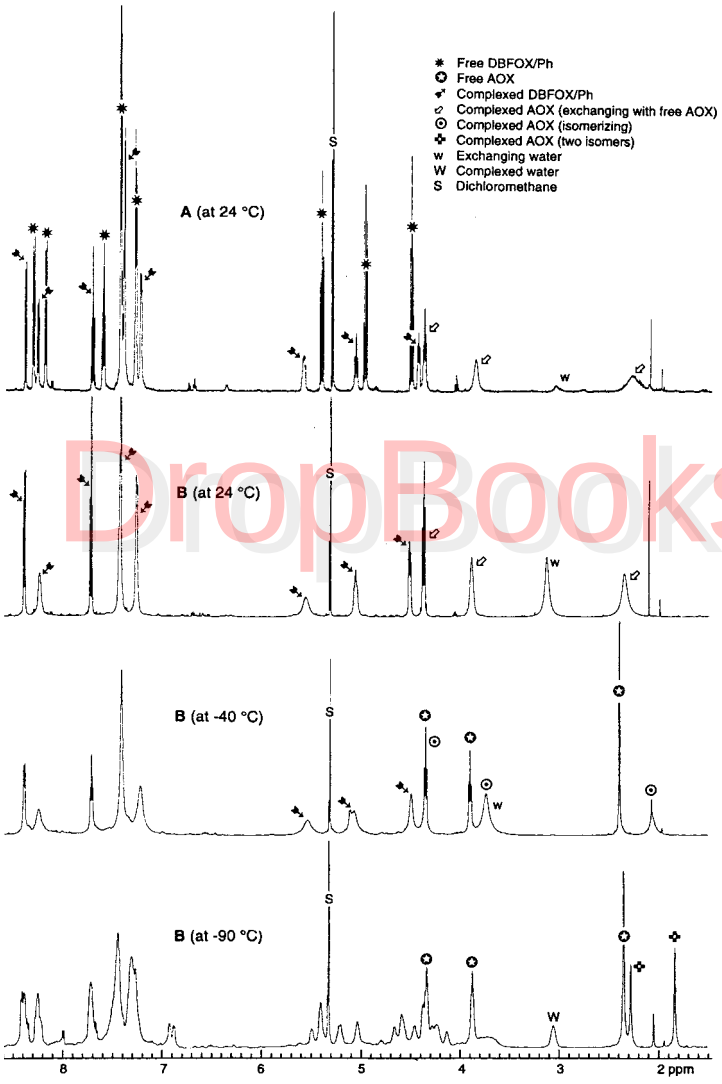


Scheme 7.9

The anhydrous zinc(II) complex **G** was prepared by treating *R,R*-DBFOX/Ph ligand with anhydrous ZnI_2 and $AgClO_4$ (in a 1:1:2 molar ratio) in dry deuterodichloromethane followed by filtration of the resulting AgI by the aid of a syringe filter; the aqua complex **H** was prepared from *R,R*-DBFOX/Ph and $Zn(ClO_4)_2 \cdot 6H_2O$ (in a 1:1 molar ratio). To prepare a clear solution of the above catalyst complexes, the presence of 3-acetyl-2-oxazolidinone (referred to as AOX) as chelating ligand is essential since slow aggregation takes place in the absence of 3-acetyl-2-oxazolidinone, precipitating a colorless solid.

When an excess amount of AOX (1.4 equiv.) was used in the formation of anhydrous complex **G**, one set of signals was only observed for AOX. This indicates that the free and complexed AOXs are rapidly exchanging (Scheme 7.10, spectrum B at 24 °C). On the other hand, the free and complexed DBFOX/Ph ligands were observed as clearly separated set of signals when *R,R*-DBFOX/Ph was used in excess (1.7 equiv., spectrum A). Thus, it is clear that the *R,R*-DBFOX/Ph·$Zn(ClO_4)_2$ complex has a much higher stability than the $(AOX)_n \cdot Zn(ClO_4)_2$ complex. It is

noteworthy to emphasize that *R,R*-DBFOX/Ph and AOX are both neutral ligands. Such high stability of the *R,R*-DBFOX/Ph·$Zn(ClO_4)_2$ complex and rapid exchange of AOX must have been favored to achieve high enantioselectivity in asymmetric reactions catalyzed by a *R,R*-DBFOX/Ph complex.



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Scheme 7.10

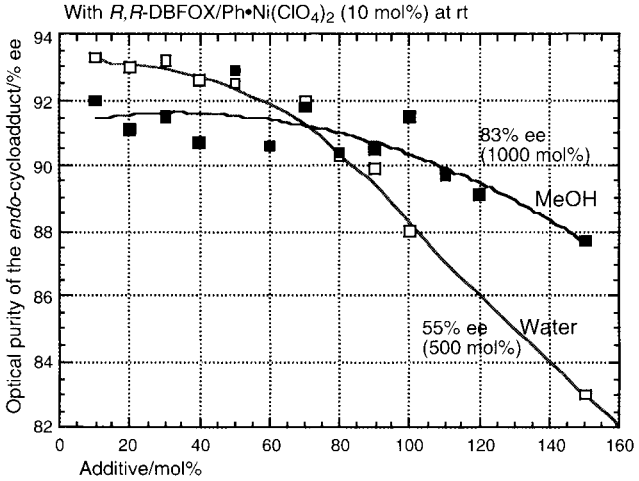
At –40 °C, signals of AOX became separated as two sets for the free and complexed species (spectrum B at –40 °C) where the complexed AOX was rapidly isomerizing between two diastereomeric complexes. At –90 °C, acetyl moiety of the complexed AOX was observed separately as two singlet signals with an intensity of ca 1 : 1 ratio, and concurrently all the protons that belong to the oxazoline and oxazolidine rings became diastereotopic (spectrum B at –90 °C). Apparently, the isomerization was restricted at this temperature. Based on the effect of water content discussed below, these two signals of acetyl group can be assigned to the diastereomeric octahedral structures **Ia** and **Ib** (Scheme 7.9). This isomerization should take place through a trigonal bipyramid intermediate **Ic** with a low energy barrier.

When the aqua complex catalyst *R,R*-DBFOX/Ph·$Zn(ClO_4)_2 \cdot 3H_2O$ **H** was employed instead of the anhydrous catalyst **G**, simple substrate complexes were again formed at each temperature. In this case, however, the free AOX was separately observed from the complexed AOX even at room temperature. This makes a striking contrast with the case of anhydrous complex **G** in which the coordination/liberation process was only restricted at –40 °C. It is likely that the presence of aqua ligand(s) on the zinc ion of the complex increases the activation energy in the coordination/liberation process of AOX ligand. The intensity of the free AOX relatively increased because of the competitive coordination of water. At –80 °C, two separated AOX ligands were observed in ca 1 : 1 ratio again. Both can be assigned to the complexed AOX. Based on the remarkable water effect on the activation energy as well as the unchanged isomer ratio (ca 1 : 1), it is proposed that these two isomers of complexed AOX observed at –80 °C have octahedral complex structures **Ia** and **Ib**.

7.2.4
Tolerance of the Catalysts

Effect of water additive was examined in the asymmetric Diels-Alder reactions catalyzed by the *R,R*-DBFOX/Ph·$Ni(ClO_4)_2$ complex. After addition of an appropriate amount of water to the anhydrous complex **A**, the reaction with an excess amount of cyclopentadiene was performed at room temperature. Enantioselectivity was as high as 93% ee for the *endo* cycloadduct up to five equivalents of water added and the satisfactory level of 88% ee was maintained when 10 equivalents were added. However, enantioselectivity gradually decreased with the increased amounts of water added: 83 and 55% ee from 15 and 50 equivalents, respectively (Scheme 7.11). When the reaction temperature went down to –40 °C, the enantioselectivity as high as 98% ee resulted up to 15 equivalents of water additive. The effect of methanol at room temperature was even more surprising. In the presence of 15 and 100 equivalents of methanol, high levels of enantioselectivities of 88% and 83% ee, respectively, were recorded for the reactions at room temperature.

The effects of a variety of acids and amines are summarized in Scheme 7.12. As long as amounts of these amine additives are limited to three equivalents to



Scheme 7.11

R,R-DBFOX/Ph•Ni(ClO_4)$_2$ (10 mol%) at rt

Additive	Mol%	Time/h	Yield/%	*endo:exo*	% ee
$PhNH_2$	30	0.7	74	91/9	91
$PhCH_2NH_2$ ppt	30	0.7	46	94/6	90
Pyridine	30	0.7	83	95/5	86
2,4,6-Collidine ppt	30	0.7	95	92/8	93
Et_2NH	30	1.2	75	90/10	1
MeCOOH	10	0.7	84	97/3	91
MeCOOH	60	0.7	92	91/9	88
PhCOOH	10	0.7	97	93/7	91
PhCOOH	60	0.7	97	92/8	81
p-$NO_2C_6H_4COOH$	10	0.7	98	93/7	91
PhOH	60	0.7	98	94/6	92

Scheme 7.12

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the catalyst *R,R*-DBFOX/Ph·Ni(ClO_4)$_2$, high levels of enantioselectivities can be obtained for the *endo* cycloadduct. The only exception was the reaction in the presence of diethylamine, where the cycloadduct was racemic.

7.2.5 Nonlinear Effect

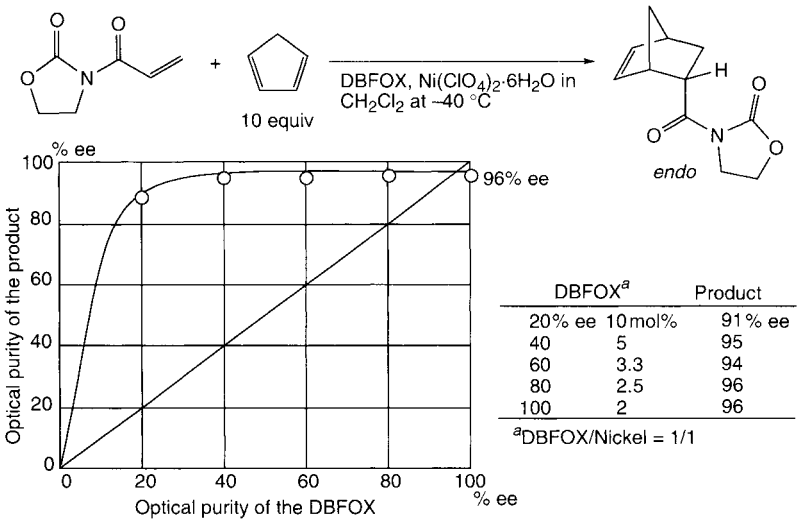
The three water ligands located at meridional positions of the *R,R*-DBFOX/Ph aqua complexes may be replaced by another molecule of DBFOX/Ph ligand if steric hindrance is negligible. Based on molecular model inspection, the heterochiral enantiomer *S,S*-DBFOX/Ph looks like a candidate to replace the water ligands to form the heterochiral *meso*-2:1 complex *R,R*-DBFOX/Ph·*S,S*-DBFOX/

Ph · $Ni(ClO_4)_2$. However, the 2 : 1 complex containing a homochiral pair, two molecules of *R,R*-DBFOX/Ph, can be never formed because of the supposed severe steric hindrance between the 4-phenyl substituents of oxazoline rings. When a catalyst complex is prepared from DBFOX/Ph ligand of a low enantiomeric purity, formation of heterochiral *meso*-2 : 1 complex *R,R*-DBFOX/Ph · *S,S*-DBFOX/Ph · $Ni(ClO_4)_2$ is expected, and that the resulting *meso* complex with saturated coordination should be inert in catalytic activity. If this happens, part of minor enantiomer of DBFOX/Ph ligand is consumed to enrich enantiomeric purity of the remaining ligand, indicating a possibility of effective chiral amplification [59–65].

A catalyst was prepared in-situ from $Ni(ClO_4)_2 \cdot 6H_2O$ (20 mol%) and DBFOX/Ph of a low enantiomeric purity (20% ee, *R,R*: 12 mol%; *S,S*: 8 mol%) under stirring in dichloromethane at room temperature for 2 h. During this procedure, the nickel salt became gradually dissolved in the solution, but at a late stage of this procedure some pale blue solid started to precipitate. Without removal of this solid, the resulting suspension was employed in the Diels-Alder reaction between cyclopentadiene (10 equiv.) and 3-acryloyl-2-oxazolidinone at –40 °C for 72 h. Cycloadduct was obtained in 95% yield (*endo*/*exo* = 97 : 3) with an enantioselectivity as high as 96% ee for the *endo* cycloadduct. Schemes 7.13 and 7.14 show the relationship between the enantiomeric purity of DBFOX/Ph ligand used and the enantioselectivity observed for the *endo* cycloadduct, where the ratio of DBFOX/Ph to $Ni(ClO_4)_2 \cdot 6H_2O$ is 1 : 1 mol/mol and a catalytic loading is 2 mol% for the excess enantiomer of the ligand. With the DBFOX/Ph ligand of 20% ee, a 91% ee was recorded for the *endo* cycloadduct, and 95% ee was recorded from 40% ee ligand. One should recognize that the excellent levels of chiral amplification have been attained, since the maximum enantioselectivity was 96% ee (*endo*) which could be attained in the reaction using the pure enantiomer of *R,R*-DBFOX/Ph ligand (2 mol%) at –40 °C. This means that the reaction has been catalyzed by the almost pure enantiomer of complex **A** which remained in the solution by an absolutely effective chirality enrichment process.

When the ligand DBFOX/Ph of a low enantiomeric purity was used for complex formation, the pale blue solid was rapidly precipitated. This product has a molecular formula of the monohydrate of $(DBFOX)_2 \cdot Ni(ClO_4)_2$ (by elemental analysis) consisting of a pair of heterochiral DBFOX/Ph ligands. A CD spectrum recorded in 1,2-dichloroethane containing a small amount of DMSO showed no absorption. The structure was assigned to be an S_4-symmetric *meso* structure, as confirmed by X-ray single crystallography analysis (Scheme 7.15). The most straightforward access to the *meso*-2 : 1 complex is the treatment of 1 : 1 adduct *R,R*-DBFOX/Ph · $Ni(ClO_4)_2 \cdot 3H_2O$ with the other enantiomer of free ligand *S,S*-DBFOX/Ph, and this actually took place quantitatively.

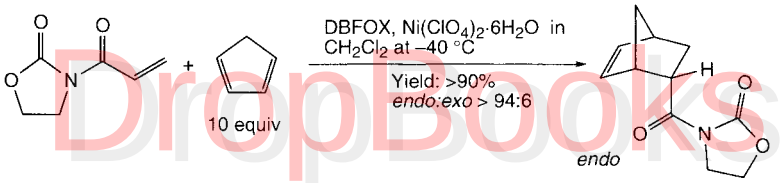
The *meso*-2 : 1 complex is sparingly soluble in most organic solvents, but it has limited solubility in DMSO and DMF. No decomposition occurs even on heating in wet DMSO or DMF. Accordingly, once the *meso*-2 : 1 complex was formed in the step of complex formation, no dissociation into components, DBFOX/Ph and $Ni(ClO_4)_2 \cdot 6H_2O$, took place, formation of *meso*-2 : 1 complex being irreversible. The following experiments provide some supporting evidence for the inactivity of *meso*-2 : 1 complex:



DBFOX[a]		Product
20% ee	10 mol%	91% ee
40	5	95
60	3.3	94
80	2.5	96
100	2	96

[a]DBFOX/Nickel = 1/1

Scheme 7.13



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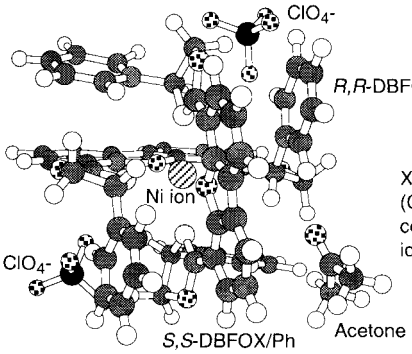
Entry	DBFOX/Ph	Ni	Ligand	Major	Minor	ee %
		mol%				
1	20 %ee	10	10	6	4	91
2[a]	20	10	10	6	4	94
3	20	20	20	12	8	96
4	20	20	10	6	4	85
5	20	10	20	12	8	58
6	40	5	5	3.5	1.5	95
7	50	10	10	7.5	2.5	95
8	50	10	20	15	5	94
9	50	10	40	30	10	58
10	60	3.3	3.3	2.6	0.7	94
11	80	2.2	2.5	2.2	0.3	96
12	80	10	10	9	1	98
13	80	10	20	18	2	98
14	100	20	10	10	0	>99

[a]Both enantiopure 1:1 complexes were used.

Scheme 7.14

(i) When the isolated *meso*-2:1 complex (4 mol%) was pretreated with a mixture of $Ni(ClO_4)_2 \cdot 6H_2O$ (16 mol%) and the pure enantiomer of *R,R*-DBFOX/Ph·$Ni(ClO_4)_2 \cdot 3H_2O$ (2 mol%) in dichloromethane, a high chiral induction was recorded (97% ee for the *endo* cycloadduct) in the Diels-Alder reaction at –40 °C.



X-Ray deterimined stereostructure (Chem 3D drawn) of *meso*-2:1 complex which contains two ClO_4^- ion and an acetone molecule.

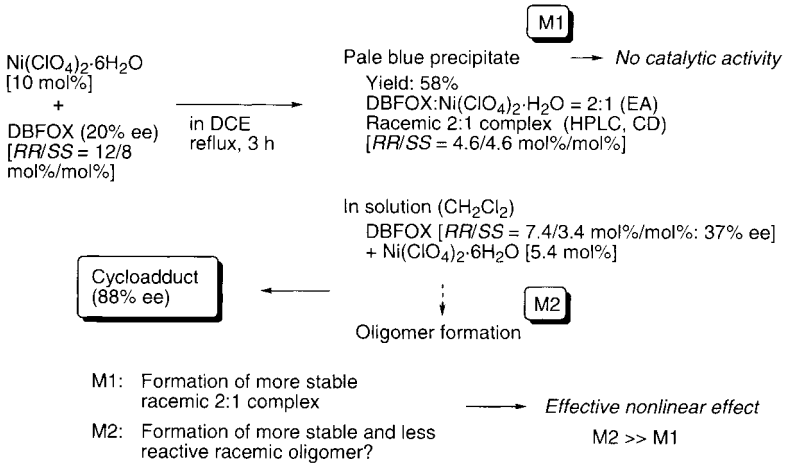
Scheme 7.15

(ii) The Diels-Alder reaction was not accelerated by a mixture of the isolated *meso*-2:1 complex (4 mol%) and the pure enantiomer of *R,R*-DBFOX/Ph (5 mol%).

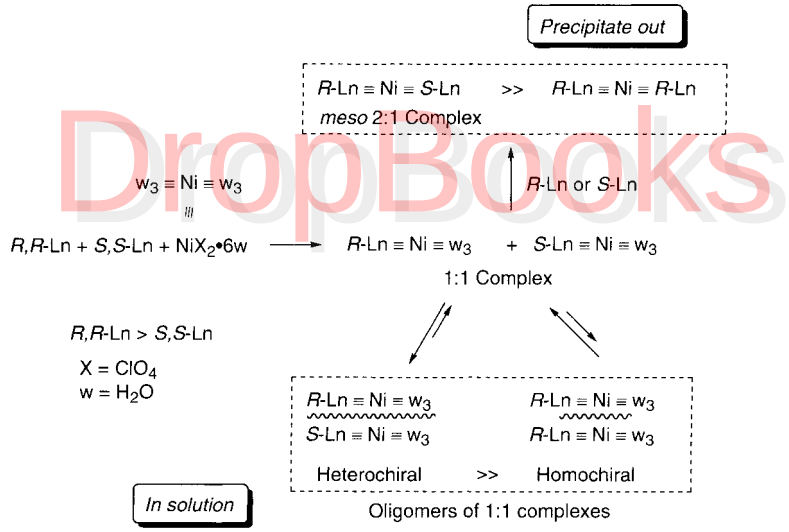
By irreversible formation of *meso*-2:1 complex, the major enantiomer of the DBFOX/Ph ligand can be enriched in the solution so that the enantioselectivity for the *endo* cycloadduct should exceed the enantiomeric purity of the DBFOX/Ph ligand used. However, even when the complex formation was performed under reflux in 1,2-dichloroethane to effect the 2:1 complex formation, the yield of *meso*-2:1 complex was only 58% yield (Scheme 7.16). Enantiomeric purity of DBFOX/Ph ligand remaining in the solution was calculated to be 37% ee, while the enantioselectivity actually observed for the *endo* cycloadduct was 88% ee. Apparently a chirality enrichment mechanism other than that through the precipitation of *meso*-2:1 complex exists in the solution. The formation of *meso*-2:1 complex proceeds through the reaction of 1:1 complex with free DBFOX/Ph ligand, and hence this transformation is limited to occur in an early stage of complex formation. When all the free ligand DBFOX/Ph is consumed, the production of *meso*-2:1 complex ceases (Scheme 7.17).

When equivalent amounts of $Ni(ClO_4)_2 \cdot 6H_2O$ and DBFOX/Ph are used in the catalyst preparation process, two molecules of ligand DBFOX/Ph are consumed to form heterochiral *meso*-2:1 complex so that $Ni(ClO_4)_2 \cdot 6H_2O$ becomes excess toward the ligand in the solution. The presence of excess-free metal salt $Ni(ClO_4)_2 \cdot 6H_2O$ appears to be unfavorable since the competitive reaction catalyzed by achiral catalyst should affect the enantioselectivity of reaction. However, the results indicate that this is not actually a serious problem. In the absence of DBFOX/Ph ligand, $Ni(ClO_4)_2 \cdot 6H_2O$ is hardly soluble in dichloromethane. This solubility advantage is supported by two observations:

(i) No rate acceleration is observed in the Diels-Alder reaction catalyzed by $Ni(ClO_4)_2 \cdot 6H_2O$ in the absence of DBFOX/Ph ligand. 3-Acryloyl-2-oxazolidinone as chelating reagent can not solubilize the nickel salt.
(ii) Even the reaction using excess $Ni(ClO_4)_2 \cdot 6H_2O$ together with the enantiopure *R,R*-DBFOX/Ph gives absolute enantioselectivity.



Scheme 7.16


Precipitate out
R-Ln ≡ Ni ≡ S-Ln >> R-Ln ≡ Ni ≡ R-Ln
meso 2:1 Complex
w3 ≡ Ni ≡ w3
R-Ln or S-Ln
R,R-Ln + S,S-Ln + NiX2•6w
R-Ln ≡ Ni ≡ w3 + S-Ln ≡ Ni ≡ w3
1:1 Complex
R,R-Ln > S,S-Ln
X = ClO4
w = H2O
R-Ln ≡ Ni ≡ w3
S-Ln ≡ Ni ≡ w3
R-Ln ≡ Ni ≡ w3
R-Ln ≡ Ni ≡ w3
Heterochiral >> Homochiral
In solution
Oligomers of 1:1 complexes

Scheme 7.17

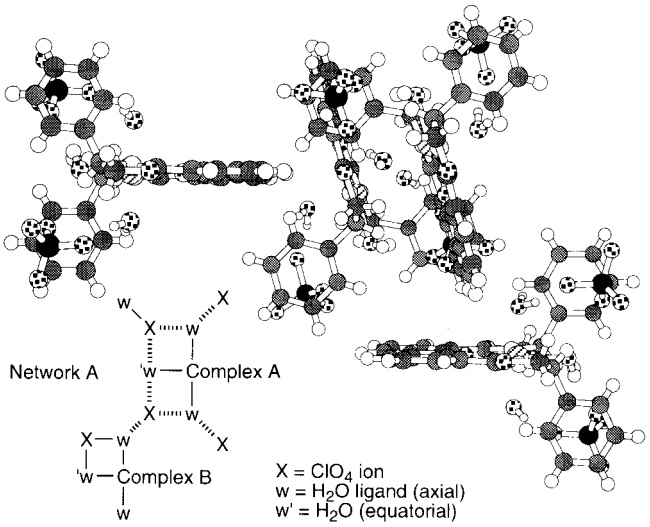
It is interesting that the use of excess ligand DBFOX/Ph led to a decreased enantioselectivity for the *endo* cycloadduct, especially when the enantiomeric purity of the ligand was low. This phenomenon is closely related with the chirality enrichment mechanism operating in the solution.

The second chirality enrichment mechanism operating in the solution is most likely that some heterochiral pairs of the 1:1 complex DBFOX/Ph·$Ni(ClO_4)_2$ are formed or they are further associated to form relatively stable racemic aggregation [58], while weak aggregation should result in the case of enantiopure 1:1 complex

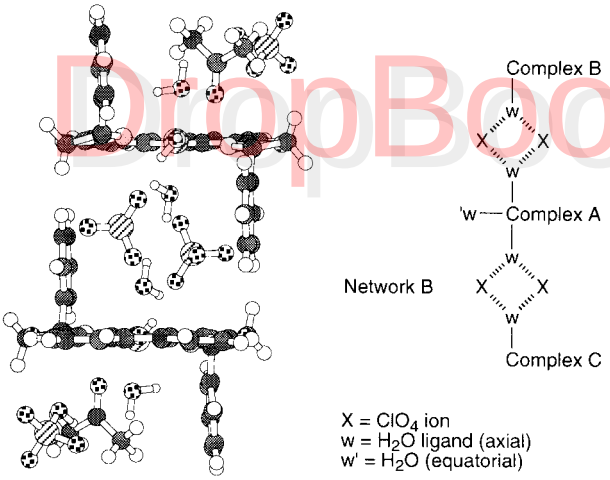
DBFOX/Ph·Ni(ClO_4)$_2$. The aqua ligands apparently play an important role in the chirality enrichment process, increasing stability of the associated heterochiral oligomers. For example, the Diels-Alder reaction using the anhydrous complex (20% ee, 10 mol%) prepared from DBFOX/Ph, $NiBr_2$, and $AgClO_4$ (1:1:2 molar ratio) only resulted in a low chiral amplification. When enantiopure 1:1 aqua complexes, *R,R*-DBFOX/Ph·Ni(ClO_4)$_2$·3H_2O and *S,S*-DBFOX/Ph·Ni(ClO_4)$_2$·3H_2O, were mixed in a ratio of 6 and 4 mol%, respectively, and used in the Diels-Alder reaction at room temperature, a 94% ee was observed for the *endo* cycloadduct. This indicates that the chiral enrichment mechanism working in the solution is much more effective.

The single crystals in each case were prepared in order to estimate the intermolecular interactions in homochiral and heterochiral aggregations of 1:1 complexes. The X-ray structure of *R,R*-DBFOX/Ph·Ni(ClO_4)$_2$·3H_2O has been shown in Scheme 7.2. On the other hand, single crystals of heterochiral pairs were prepared by the following procedure. Equivalent amounts of each enantiopure 1:1 complexes *R,R*-DBFOX/Ph·Ni(ClO_4)$_2$·3H_2O and *S,S*-DBFOX/Ph·Ni(ClO_4)$_2$·3H_2O were dissolved in dichloromethane containing acetone as cosolvent. After these two solutions were mixed, benzene was added. Slow evaporation of the relatively more volatile dichloromethane and acetone gave single crystals of racemic 1:1 complex. Are depicted packing structures for the enantiopure 1:1 complex *R,R*-DBFOX/Ph·Ni(ClO_4)$_2$·3H_2O (Scheme 7.18) and racemic compound *R,R*-DBFOX/Ph·Ni(ClO_4)$_2$·3H_2O/*S,S*-DBFOX/Ph·Ni(ClO_4)$_2$·3H_2O (Scheme 7.19). Single crystals prepared from enantiopure 1:1 complexes include four molecules of *R,R*-DBFOX/Ph·Ni(ClO_4)$_2$·3H_2O in a unit cell, in which two each are parallel with a layer distance of 7.41 Å (Scheme 7.18). We assume that intermolecular attractive interactions should be working through hydrogen bonds between the water ligands and perchlorate ions in the network. Measurement of the oxygen-oxygen distances between water ligand and perchlorate ion should be informative. However, the perchlorate ion has a spherical shape with high mobility so that temperature factor for this anion is relatively big as shown in Scheme 7.18. Accordingly, we used the distance between a chlorine atom of perchlorate and an oxygen atom of water to evaluate hydrogen bond interactions. We hypothesize that such an attractive interaction should exist when the distance is shorter than 4 Å. Each perchlorate ion is bonded with an equatorial and an axial water ligands of the same molecule of 1:1 complex and these axial waters are bonded with perchlorate ions which belong to the adjacent molecules (network A in Scheme 7.18, the oxygen-chlorine distances are 3.91, 3.79, 3.75, 3.72, and 3.67 Å). As a result, the two adjacent 1:1 complexes are linked with one hydrogen bond.

On the other hand, in the single crystals prepared from equivalent amounts of heterochiral 1:1 complexes, a pair of two heterochiral 1:1 complexes are incorporated in a unit cell to form a layered structure with alternate layer distances of 7.33 and 7.6 Å. Two perchlorate ions stay in the narrower gap, and two additional acetone molecules as crystallization solvent occupy the wider gap. The perchlorate ions interact with two axial water ligands by hydrogen bonds (3.71 and 3.77 Å) to construct a layered structure. The adjacent two molecules of heterochiral 1:1 com-



Scheme 7.18



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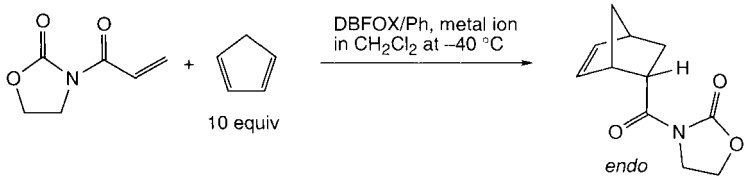
Scheme 7.19

plexes, *R,R*-DBFOX/Ph·Ni$(ClO_4)_2 \cdot 3H_2O$ and *S,S*-DBFOX/Ph·Ni$(ClO_4)_2 \cdot 3H_2O$, interact with each other by two hydrogen bonds per one complex molecule. This suggests that heterochiral aggregation should be much stronger than the above homochiral case.

We believe that the 1:1 complex *R,R*-DBFOX/Ph·Ni$(ClO_4)_2 \cdot 3H_2O$ (supposed to be major enantiomer) would interact, even in the solution, with heterochiral 1:1 complex *S,S*-DBFOX/Ph·Ni$(ClO_4)_2 \cdot 3H_2O$ much stronger than homochiral 1:1 complex *R,R*-DBFOX/Ph·Ni$(ClO_4)_2 \cdot 3H_2O$. As a result, the minor complex is deac-

tivated in the solution to enrich the major enantiomer of 1:1 complex *R,R*-DBFOX/Ph·$Ni(ClO_4)_2 \cdot 3H_2O$. This is the mechanism for effective chiral amplification occurring in the solution. Such differential of stabilization of oligomeric forms is supported by the observation that crystals of the enantiopure 1:1 complex rapidly dissolved in dichloromethane when treated with 3-acetyl-2-oxazolidine, whereas those of racemic complex were not soluble even under harder conditions.

The relative stability between homochiral and heterochiral aggregations of 1:1 complexes should depend upon the polarity of solvents or additives used. We have mentioned above that the addition of coordinating additives such as diethyl ether, acetone, and 1,2-dichloroethane works to activate the DBFOX complex-catalyzed Diels-Alder reactions (Scheme 7.20). We therefore examined solvent and additive effects for chiral amplification. A low level of chiral amplification resulted in the presence of acetone, meaning that acetone is powerful enough to dissociate the strong heterochiral oligomers. Hydrogen bonds of aqua ligands to SbF_6 anions are similarly effective as perchlorate ions. Although aqua complexes of magnesium, ion(II), and copper(II) perchlorates are not proper choice for high chiral amplification, zinc perchlorate showed even a more effective amplification than nickel perchlorate (94% ee from 20% ee). Thus, the complex was prepared from DBFOX/Ph (20% ee, 10 mol%) and ZnI_2 in dichloromethane, followed by treatment of $AgClO_4$ (20 mol%). After 3 equivalents of water were added, the catalyst was used in the Diels-Alder reaction at –40 °C to give the enantiomeric activity of 96% ee (quantitative, *endo*/*exo*=98:2) for the *endo* cycloadduct. Thus, the absolute or theoretically maximum chiral amplification has been attained.



Entry	Metal salts	DBFOX/Ph	Ni (mol%)	Ligand (mol%)	Time	Yield	*endo:exo*	ee %
1[a]	$Ni(ClO_4)_2 \cdot 6H_2O$	20 %ee	10	20	48 h	quant	97/3	52
2[b]	$Ni(ClO_4)_2 \cdot 6H_2O$	20	10	20	48	62 %	96/4	19
3[c]	$Ni(ClO_4)_2 \cdot 6H_2O$	20	10	10	18	80	97/3	28
4	$Ni(SbF_6)_2 + 3H_2O$	20	10	20	12	quant	97/3	54
5	$Mg(ClO_4)_2$	20	10	10	48	98	86/14	20
6	$Mg(ClO_4)_2$	50	10	20	144	91	97/3	40
7	$FeCl_2 + 2AgClO_4 + 3H_2O$	20	10	10	96	quant	98/2	47
8	$CuCl_2 + 2AgClO_4 + 3H_2O$	20	10	10	96	96	97/3	87
9	$ZnI_2 + 2AgClO_4 + 3H_2O$	20	10	10	96	quant	98/2	94

[a]Solvent: CH_2Cl_2/Et_2O = 4:1 v/v. [b]Solvent: CH_2Cl_2/Acetone = 4:1 v/v. [c]Additive: NH_2NH_2 (4 mol%).

Scheme 7.20

7.3 Nitrone and Nitronate Cycloadditions

1,3-Dipolar cycloadditions are one of the most useful synthetic methods to make stereochemically defined five-membered heterocycles. Although a variety of diastereoselective 1,3-dipolar cycloadditions have been well developed, enantioselective versions are still limited [29]. Nitrones are important 1,3-dipoles that have been the target of catalyzed enantioselective reactions [66]. Three different approaches to catalyzed enantioselective reactions have been taken: (1) activation of electron-deficient alkenes by a chiral Lewis acid [23–26, 32–34, 67], (2) activation of nitrones in the reaction with ketene acetals [30, 31], and (3) coordination of both nitrones and allylic alcohols on a chiral catalyst [20]. Among these approaches, the dipole/HOMO-controlled reactions of electron-deficient alkenes are especially promising because a variety of combinations between chiral Lewis acids and electron-deficient alkenes have been well investigated in the study of catalyzed enantioselective Diels-Alder reactions. Enantioselectivities in catalyzed nitrone cycloadditions sometimes exceed 90% ee, but the efficiency of catalytic loading remains insufficient.

The aqua complex derived from (*R,R*)-4,6-dibenzofuranidyl-2,2′-bis(4-phenyloxazoline) ligand (*R,R*-DBFOX/Ph) and $Ni(ClO_4)_2 \cdot 6H_2O$ was found to act as excellent chiral Lewis acid catalyst in asymmetric 1,3-dipolar cycloadditions of nitrones to 3-(2-alkenoyl)-2-oxazolidinones in the presence of MS 4 Å [68]. The observed enantioselectivity of >99% and the minimum catalytic loading of 2 mol% are much more effective than previous examples. The presence of MS 4 Å is essential to attain high selectivities. The results are satisfied by an *endo* approach of *Z* isomers of nitrones leading to 3,4-*trans*-isoxazolidines with 4*R*,5*S* absolute configurations. The effect of water on both *endo* selectivity and enantioselectivity can be explained by involving the transition structure including a substrate complex of trigonal bipyramid geometry.

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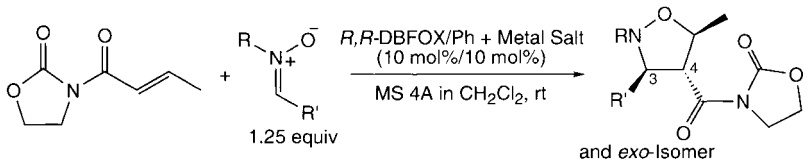
7.3.1 Nickel(II) Complex-catalyzed Reactions

Among the *R,R*-DBFOX/Ph-transition(II) metal complex catalysts examined in nitrone cycloadditions, the anhydrous *R,R*-DBFOX/Ph complex catalyst prepared from $Ni(ClO_4)_2$ or $Fe(ClO_4)_2$ provided equally excellent results. For example, in the presence of 10 mol% of the anhydrous nickel(II) complex catalyst *R,R*-DBFOX/Ph·$Ni(ClO_4)_2$, which was prepared in-situ from *R,R*-DBFOX/Ph ligand, $NiBr_2$, and 2 equimolar amounts of $AgClO_4$ in dichloromethane, the reaction of 3-crotonoyl-2-oxazolidinone with *N*-benzylidenemethylamine *N*-oxide at room temperature produced the 3,4-*trans*-isoxazolidine (63% yield) in near perfect *endo* selectivity (*endo*/*exo* = 99:1) and enantioselectivity in favor for the 3*S*,4*R*,5*S* enantiomer (>99% ee for the *endo* isomer, Scheme 7.21). The copper(II) perchlorate complex showed no catalytic activity, however, whereas the ytterbium(III) triflate complex led to the formation of racemic cycloadducts.

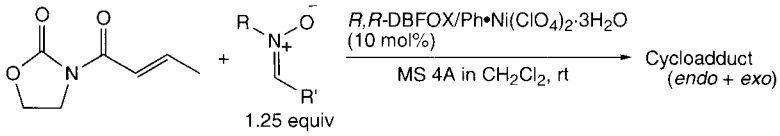


R	R'	Metal salt/mol%	Time/h	Yield/%	*endo/exo*	ee %
Ph	*p*-MeOC$_6$H$_4$	$CuCl_2$/10, $AgClO_4$/20	96	0	-	-
Ph	*p*-MeOC$_6$H$_4$	$Yb(OTf)_3 \cdot H_2O$	72	95	83/17	0
Ph	*p*-MeOC$_6$H$_4$	ZnI_2/10, $AgClO_4$/20	72	55	87/13	86
Ph	*p*-MeOC$_6$H$_4$	$FeCl_2$/10, $AgClO_4$/20	72	77	93/7	90
Ph	*p*-MeOC$_6$H$_4$	$NiBr_2$/10, $AgClO_4$/20	96	87	95/5	89
Ph	*p*-MeOC$_6$H$_4$	$Ni(ClO_4)_2 \cdot 6H_2O$/10	72	quant	>99/1	87
Me	Ph	$Mg(ClO_4)_2$/10	96	quant	62/38	71
Me	Ph	$NiBr_2$/10, $AgClO_4$/20	72	63	99/1	>99
Me	Ph	$FeCl_2$/10, $AgClO_4$/20	72	69	95/5	>99
Me	Ph	$Ni(ClO_4)_2 \cdot 6H_2O$/10	72	72	98/2	>99

Scheme 7.21

The aqua nickel(II) complex *R,R*-DBFOX/Ph·$Ni(ClO_4)_2 \cdot 3H_2O$ gave rise to comparably excellent selectivities (72%, *endo*/*exo*=98:2, >99% ee for the *endo* cycloadduct) in a similar reaction using the same combination of substrates in the presence of MS 4 Å. The aqua nickel(II) complex catalyst, which can be easy to prepare from the commercially available and inexpensive nickel perchlorate hexahydrate, can be stored for months in open air without loss of catalytic activity. Or, this catalyst can be simply prepared in-situ by stirring equimolar amounts of the *R,R*-DBFOX/Ph ligand and $Ni(ClO_4)_2 \cdot 6H_2O$ at room temperature in dichloromethane for a few hours. The simple preparation procedure of the aqua nickel(II) complex catalyst should be attractive.

Reactions of other nitrones with 3-crotonoyl-2-oxazolidinone are also diastereoselective (*endo*/*exo* ≥95:5) and enantioselective for the *endo* cycloadducts (Scheme 7.22). High efficiency of the catalytic cycle can be demonstrated in the reactions of *N*-(*p*-methoxybenzylidene)benzylamine *N*-oxide: a 99% ee for the *endo* cycloadduct was recorded with 2 mol% of the catalyst at room temperature and a 93% ee with 1 mol% even under reflux in dichloromethane. The nitrone having a bulky aromatic *C*-substituent such as *N*-(1-naphthylidene)aniline *N*-oxide showed a decreased reactivity, the chemical yield, diastereoselectivity, and enantioselectivity being all poor, while the isomer *N*-(2-naphthylidene)aniline *N*-oxide was sufficiently reactive. It was pleasing that the nitrone derived from an aliphatic aldehyde, *N*-propylidenebenzylamine *N*-oxide, also showed excellent diastereoselectivity as well as enantioselectivity for the *endo* cycloadduct. Thus, the DBFOX/Ph·$Ni(ClO_4)_2 \cdot 3H_2O$ catalyzed asymmetric nitrone cycloaddition in the presence of MS 4 Å has the most promising features with respect to the catalytic cycle, diastereoselectivity, and enantioselectivity among the catalyzed reactions yet reported.



R	R'	Temp/°C	Yield/%	*endo/exo*	ee %
Ph	Ph	rt	96	98/2	89
Ph	*p*-MeC$_6$H$_4$	rt	quant	99/1	>99
Me	Ph	rt	72	98/2	>99
Bn	Ph	rt	76	>99/1	94
Bn	*p*-MeOC$_6$H$_4$	rt	73	>99/1	>99
Bn	*p*-MeOC$_6$H$_4$	rt	75	>99/1	99[a]
Bn	*p*-MeOC$_6$H$_4$	reflux	37	>99/1	93[b]
Ph	2-Naphthyl	rt	quant	99/1	45
Ph	1-Naphthyl	rt	25	74/26	9
Bn	Et	rt	92	94/6	97

Catalytic loading: [a]2 mol%, [b]1 mol%.

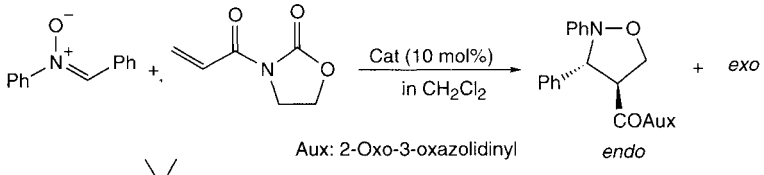
Scheme 7.22

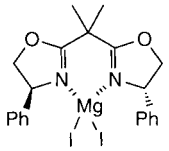
7.3.2 Role of MS 4 Å

In the Lewis acid-catalyzed asymmetric cycloaddition reactions of nitrones, it is found that the use of MS 4 Å is essential to attain high selectivities, and in some cases, the switch of enantioselectivities has been observed. Jørgensen and co-workers reported that the reactions of *N*-benzylideneaniline *N*-oxide with 3-crotonoyl-2-oxazolidinone catalyzed by the bisoxazoline-magnesium complexes exhibited the reverse mode of enantioselectivities in the presence and absence of MS 4 Å (Scheme 7.23) [28]. The enantioselectivity changed in the reactions of 3-acryloyl-2-oxazolidinone depending upon the amount of MS 4 Å used. MS 3 Å and MS 5 Å work as well as MS 4 Å and no dramatic change of efficiency for the enantioselectivity switch has been observed. On the other hand, the presence of magnesium sulfate was totally ineffective, indicating that MS 4 Å was not simply working as a dehydrating agent.

Kobayashi and co-workers reported similar enantioselectivity switch in the binol-yterrbium(III) triflate complex-catalyzed cycloaddition reactions [69] between *N*-benzylidenebenzylamine *N*-oxide and 3-crotonoyl-2-oxazolidinone [70]. The reaction in the presence of MS 4 Å showed an exclusively high enantioselectivity of 96% ee, while that in the absence of MS 4 Å (–50% ee) or in the presence of pyridine *N*-oxide (–83% ee) had the opposite enantioselectivity (Scheme 7.24). This chirality switch happens generally for the combination of a wide variety of nitrones and dipolarophiles.

In the nitrone cycloaddition reactions catalyzed by the *R,R*-DBFOX/Ph transition metal complexes also, the diastereo- and enantioselectivities were found to depend upon the presence of MS 4 Å [71]. Thus, both the selectivities were much lowered in the iron(II) or nickel(II) complex-catalyzed reactions without MS 4 Å,

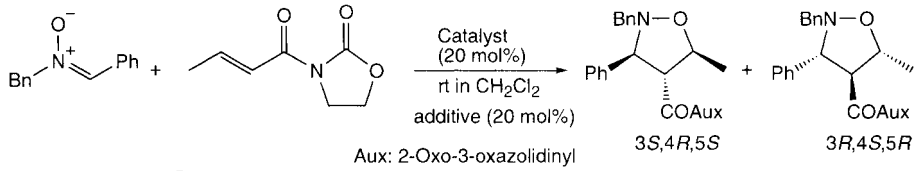


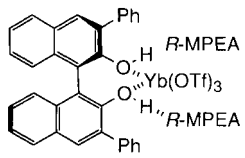


Chiral catalyst

	endo:exo	% ee/endo
MS 4A (50 mg)	73:27	82 (3*S*,4*R*)
MS 4A (10 mg)	77:23	42 (3*S*,4*R*)
MS 3A (50 mg)	73:27	82 (3*S*,4*R*)
MS 5A (50 mg)	73:27	83 (3*S*,4*R*)
$CaSO_4$ (500 mg)	80:20	41 (3*S*,4*R*)
none	100:0	48 (3*R*,4*S*)
water (20 mol%)	90:10	36 (3*R*,4*S*)
$MgSO_4$ (50 mg)	96:4	52 (3*R*,4*S*)

Scheme 7.23



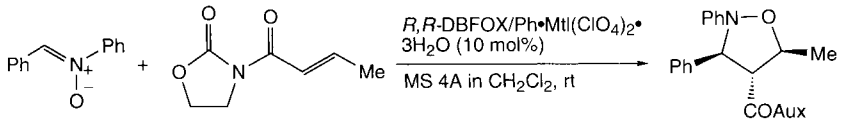


Chiral catalyst

Additive	Yield	endo:exo	% ee/endo	Configuration
MS 4A	92%	99:1	96	3*R*,4*S*,5*R*
none	83	98:2	50	3*S*,4*R*,5*S*
H_2O	81	95:5	8	3*S*,4*R*,5*S*
Pyridine *N*-oxide	90	>99:1	83	3*S*,4*R*,5*S*

Scheme 7.24

but no switch of the mode of enantioselectivity was observed unlike the two cases mentioned above (Scheme 7.25). When magnesium sulfate was used instead of MS 4 Å in the nickel(II) complex-catalyzed reaction, equally excellent *endo* and enantioselectivities were achieved, indicating that MS 4 Å worked simply as a dehydrating agent in this case. This is very different from the case observed by Jørgensen's group [28]. It is concluded on the basis of these results that the transition state structure having a trigonal bipyramid complex **F** (Scheme 7.7) is responsible for the high *endo* and enantioselectivities. In the presence of water, an octahedral transition state structure **D** (Scheme 7.7) may have been involved leading to poor selectivities due to ineffective chiral shielding and the diminished steric demand for the selective formation of the *endo* cycloadduct [57].



MS 4A:
500 mg/1 mmol scale

		Yield/%	*endo:exo*	% ee (*endo*)
DBFOX/Ph•Fe$(ClO_4)_2$•3H_2O	None	63	68:32	21
	MS 4A	69	95:5	>99
DBFOX/Ph•Ni$(ClO_4)_2$•3H_2O	None	53	73:27	36
	$MgSO_4$	100	97:3	99

Scheme 7.25

7.3.3
Nitronate Cycloadditions

Nitronates derived from primary nitroalkanes can be regarded as a synthetic equivalent of nitrile oxides since the elimination of an alcohol molecule from nitronates adds one higher oxidation level leading to nitrile oxides. This direct *β*-elimination of nitronates is known to be facilitated in the presence of a Lewis acid or a base catalyst [66, 72, 73]. On the other hand, cycloaddition reactions of nitronates to alkene dipolarophiles produce *N*-alkoxy-substituted isoxazolidines as cycloadducts. Under acid-catalyzed conditions, these isoxazolidines can be transformed into 2-isoxazolines through a ready *β*-elimination, and 2-isoxazolines correspond to the cycloadducts of nitrile oxide cycloadditions to alkenes [74].

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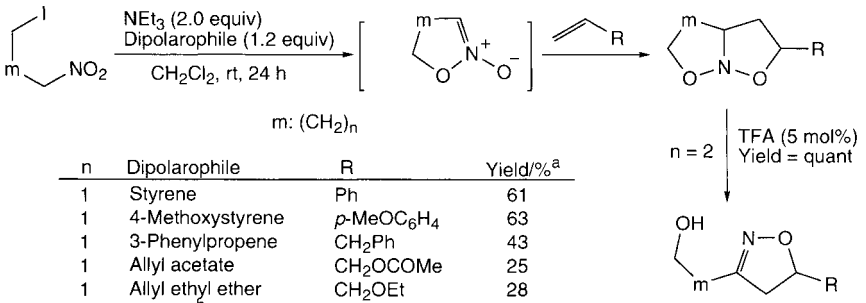
Accordingly, cyclic nitronates can be a useful synthetic equivalent of functionalized nitrile oxides, while reaction examples are quite limited. Thus, 2-isoxazoline *N*-oxide and 5,6-dihydro-4*H*-1,2-oxazine *N*-oxide, as five- and six-membered cyclic nitronates, were generated in-situ by dehydroiodination of 3-iodo-1-nitropropane and 4-iodo-1-nitrobutane with triethylamine and trapped with monosubstituted alkenes to give 5-substituted 3-(2-hydroxyethyl)isoxazolines and 2-phenylperhydro-1,2-oxazino[2,3-*b*]isoxazole, respectively (Scheme 7.26) [72b]. Upon treatment with a catalytic amount of trifluoroacetic acid, the perhydro-1,2-oxazino[2,3-*b*]isoxazole was quantitatively converted into the corresponding 2-isoxazoline. Since a method for catalyzed enantioselective nitrone cycloadditions was established and cyclic nitronates should behave like cyclic nitrones in reactivity, there would be a good chance to attain catalyzed enantioselective formation of 2-isoxazolines via nitronate cycloadditions.

We are the first group to succeed with the highly enantioselective 1,3-dipolar cycloadditions of nitronates [75]. Thus, the reaction of 5,6-dihydro-4*H*-1,2-oxazine *N*-oxide as a cyclic nitronate to 3-acryloyl-2-oxazilidinone, at –40 °C in dichloromethane in the presence of MS 4 Å and *R,R*-DBFOX/Ph · Ni(II) complexes, gave a diastereomeric mixture of perhydroisoxazolo[2,3-*b*][1,2]oxazines as the ring-fused isoxazolidines in high yields. The *R,R*-DBFOX/Ph aqua complex prepared from



n	Dipolarophile	R	Yield/%[a]
1	Styrene	Ph	61
1	4-Methoxystyrene	*p*-$MeOC_6H_4$	63
1	3-Phenylpropene	CH_2Ph	43
1	Allyl acetate	CH_2OCOMe	25
1	Allyl ethyl ether	CH_2OEt	28
2	Styrene[b]	Ph	52

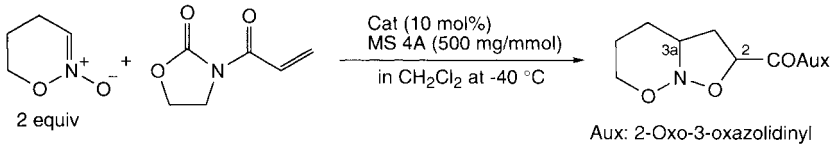
[a]Isolated yield. [b]Reaction time: 72 h.

Scheme 7.26

$Ni(ClO_4)_2 \cdot 6H_2O$ showed a little better enantioselectivity than the anhydrous complex. Although the uncatalyzed reaction was highly *exo* selective (*cis*/*trans* = 3 : 97), the catalyzed reactions were very poor in diastereoselectivity, a mixture of *endo* and *exo* cycloadducts being formed. We expected that this poor diastereoselectivity would not be a serious problem since the same enantioface should be involved at the 2-position of the diastereomeric cycloadducts (Scheme 7.27). The best enantioselectivity (*cis*: >99% ee, *trans*: 94% ee) was observed when the reaction was catalyzed by *R,R*-DBFOX/Ph · $Ni(SbF_6)_2$ (50 mol%). With the decreased amount of catalyst (10 mol%) still a satisfactory level of enantioselectivity was observed for the *cis* cycloadduct (94% ee).

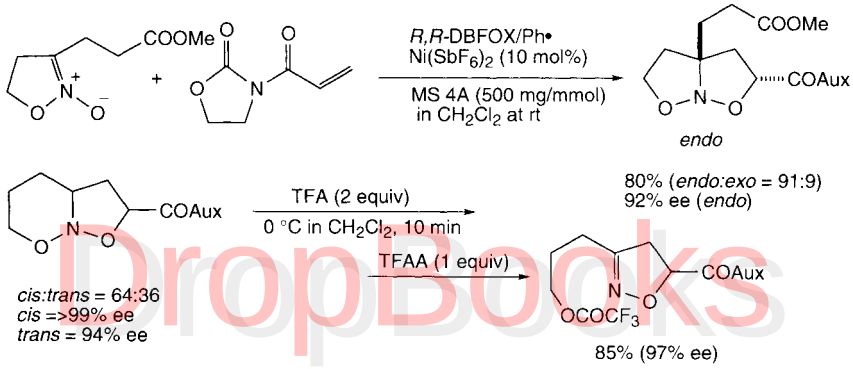
The parent five-membered nitronate having no substituent at the 3-position was too unstable to be isolated. However, 3-substituted derivatives were highly stabilized. Especially, the 3-ethyl derivatives having a terminal electron-withdrawing substituent are readily available by the dehydrochlorination of 3-chloro-1-nitropropane in the presence of electron-deficient alkenes. It was our delight that the reaction of 3-alkyl-substituted five-membered nitronates was also successfully catalyzed by *R,R*-DBFOX/Ph · $Ni(SbF_6)_2$ complex to at room temperature. This reaction was highly *endo*-selective (*cis*/*trans* = 91 : 9) and enantioselective for the *endo* cycloadduct (92% ee).

On the basis of the assumed reaction mechanism, we expected that the same enantiofaces participated in the formation of two diastereomers of cycloadducts. If our expectation is correct, both diastereomers of the ring-fused cycloadduct should provide the same enantiomer upon the ring cleavage across the O(7)–N(8) bond. Accordingly, the diastereomer mixture was submitted to the acid-catalyzed transformation to 2-isoxazoline derivative. When the mixture was treated with trifluoroacetic acid and then with trifluoroacetic anhydride, the corresponding 2-oxazoline was produced through the ring opening of isoxazine ring of the ring-fused cycloadduct in high yield with an excellent enantioselectivity (85%, 97% ee). Thus, the catalyzed asymmetric 1,3-dipolar cycloaddition of cyclic nitronates was achieved for the first time. This reaction corresponds to an equivalent to the catalyzed asymmetric cycloadditions of a functionalized nitrile oxide.



Catalyst	Time/h	Yield/%	*cis:trans*	ee % (*cis/trans*)
No catalyst	144	82	3:97	-
ZnI_2	144	92	7:93	-
R,R-DBFOX/Ph•$Mg(ClO_4)_2$	6	98	46:54	62/10
R,R-DBFOX/Ph•$Ni(ClO_4)_2$•$3H_2O$	6	90	52:48	91/61
R,R-DBFOX/Ph•$Ni(ClO_4)_2$	6	94	52:48	87/53
R,R-DBFOX/Ph•$Zn(ClO_4)_2$•$3H_2O$	24	83	23:77	23/3
R,R-DBFOX/Ph•$Mg(SbF_6)_2$	18	93	48:52	76/16
R,R-DBFOX/Ph•$Ni(SbF_6)_2$	6	97	43:57	94/60
R,R-DBFOX/Ph•$Ni(SbF_6)_2$	3	96	56:44	96/58[a]
R,R-DBFOX/Ph•$Ni(SbF_6)_2$	1	98	63:37	>99/94[b]

Catalytic amounts: [a]20 mol%, [b]50 mol%



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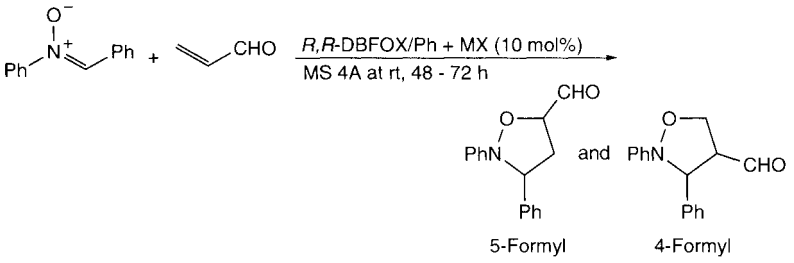
Scheme 7.27

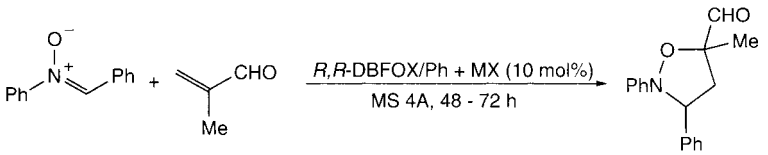
7.3.4 Reactions of Monodentate Dipolarophiles

Monodentate dipolarophiles such as acrolein, methacrolein, and α-bromoacrolein could be successfully utilized in the *R,R*-DBFOX/Ph-transition metal complex-catalyzed asymmetric nitrone cycloadditions [76]. The reactions of *N*-benzylideneaniline *N*-oxide with acrolein in the presence of the nickel(II) aqua complex *R,R*-DBFOX/Ph·$Ni(ClO_4)_2 \cdot 3H_2O$ (10 mol%) and MS 4 Å produced a mixture of two regioisomers (5-formyl/4-formyl regioisomers: ca 3:1). However, enantioselectivities for the both regioisomers were excellent when the reaction was performed at –10 °C (up to 98% ee, Scheme 7.28).

The nitrone cycloaddition reactions with methacrolein were exclusively regioselective when catalyzed by the *R,R*-DBFOX/Ph·$Ni(ClO_4)_2 \cdot 3H_2O$ in the presence of MS 4 Å leading to the 5-formyl derivative with high enantioselectivities (up to 97% ee), while the reactions catalyzed by the *R,R*-DBFOX/Ph aqua zinc(II) complex were less selective to give a mixture of two regioisomeric cycloadducts. On the other hand, α-



MX	Solvent	Temp/°C	Yield/%	5-Formyl:4-Formyl	ee %
None	Benzene	rt	92	78 (single) : 22 (71:29)	-
$Ni(ClO_4)_2 \cdot 6H_2O$	CH_2Cl_2	rt	90	75 (single) : 25 (single)	88/81
$Ni(ClO_4)_2 \cdot 6H_2O$	CH_2Cl_2	-10	75	74 (single) : 26 (95:5)	98/91

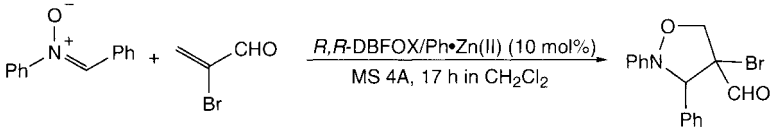


MX	Solvent	Temp/°C	Yield/%	ee %
None	Benzene	rt	61	-
$Ni(ClO_4)_2 \cdot 6H_2O$	CH_2Cl_2	rt	73	96
$Ni(ClO_4)_2 \cdot 6H_2O$	CH_2Cl_2	-10	71	97

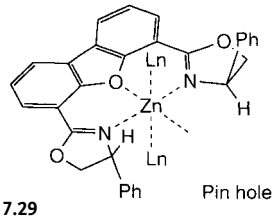
Scheme 7.28

bromoacrolein was much more reactive than methacrolein and this dipolarophile produced the 4-formyl regioisomeric cycloadducts in an exclusive regioselective manner in the nitrone cycloadditions catalyzed by the *R,R*-DBFOX/Ph complexes. Especially, the aqua zinc(II) complex *R,R*-DBFOX/Ph·$Zn(ClO_4)_2 \cdot 3H_2O$ was more effective than the anhydrous zinc(II) complex and the aqua nickel(II) complex, absolute diastereo- and enantioselectivities being observed.

It was our great surprise that the *R,R*-DBFOX/Ph complex catalysts derived from $Zn(ClO_4)_2 \cdot 6H_2O$, $Zn(OTf)_2$, and ZnI_2 were found to be equally effective as shown with the following results: $Zn(ClO_4)_2 \cdot 6H_2O$ (–40 °C, 83% yield, ds >99%, ee >99%), $Zn(OTf)_2$ (–40 °C, 94% yield, ds >99%, ee >99%), and ZnI_2 (rt, 72% yield, ds=94%, ee=95%) (Scheme 7.29). The perchlorate catalyst is cationic, while the iodide catalyst should be neutral since the zinc-iodine bond can not be readily cleaved under the reaction conditions. This indicates that the *R,R*-DBFOX/Ph·ZnI_2 catalyst should have only one vacant position for the coordination of dipolarophile and hence this catalyst belongs to a "pin hole type Lewis acid catalyst" like aluminum tris(2,6-diphenylphenoxide) (ATPh) [77]. If this is the case, the zinc iodide catalyst must have a relatively strong Lewis acidity since no aggregated form is structurally possible. We believe that the *R,R*-DBFOX/Ph-zinc(II) iodide complex catalyst has a high catalytic activity because of its monomeric form.



Catalyst	Temp/°C	Yield/%	Isomer ratio	ee %
R,R-DBFOX/Ph•Zn$(ClO_4)_2$	rt	85	83:17	90/94
R,R-DBFOX/Ph•Zn$(ClO_4)_2$•6H_2O	rt	85	88:12	95/93
R,R-DBFOX/Ph•Zn$(ClO_4)_2$•6H_2O	-40	83	single	>99/68
R,R-DBFOX/Ph•Zn$(OTf)_2$	-40	94	99:1	>99/92
R,R-DBFOX/Ph•ZnI_2	rt	72	94:6	95/84



Pin hole catalyst (Ln = nitrone or I⁻)

Scheme 7.29

7.3.5 Transition Structures

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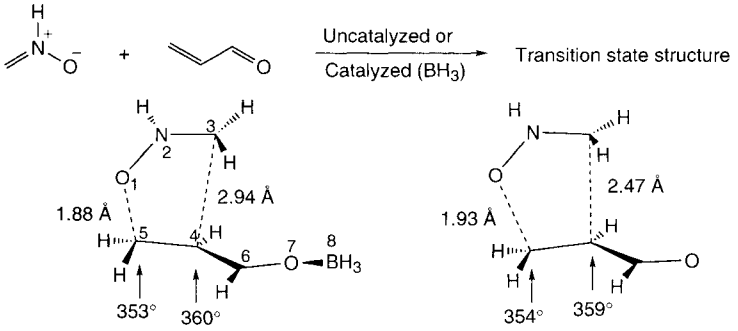
Absolute configurations of the isoxazolidines obtained in the nitrone cycloaddition reactions described in Schemes 7.21 and 7.22 were determined to be 3*S*,4*R*,5*S* structure by comparison of the optical rotations as well as retention times in a chiral HPLC analysis with those of the authentic samples. Selection of the *si* face at Cβ position of 3-crotonoyl-2-oxazolidinone in nitrone cycloadditions was the same as that observed in the Diels-Alder reactions of cyclopentadiene with 3-crotonoyl-2-oxazolidinone in the presence of the *R,R*-DBFOX/Ph·Ni$(ClO_4)_2 \cdot 3H_2O$ complex (Scheme 7.7), and this indicates that the *s-cis* conformation of the dipolarophile has participated in the reaction.

Nitrones are a rather polarized 1,3-dipoles so that the transition structure of their cycloaddition reactions to alkenes activated by an electron-withdrawing substituent would involve some asynchronous nature with respect to the newly forming bonds, especially so in the Lewis acid-catalyzed reactions. Therefore, the transition structures for the catalyzed nitrone cycloaddition reactions were estimated on the basis of ab-initio calculations using the 3-21G* basis set. A model reaction includes the interaction between CH_2=NH(O) and acrolein in the presence or absence of BH_3 as an acid catalyst (Scheme 7.30). Both the catalyzed and uncatalyzed reactions have only one transition state in each case, indicating that the reactions are both concerted. However, the synchronous nature between the newly forming O1–C5 and C3–C4 bonds in the transition structure TS-**J** of the catalyzed reaction is rather different from that in the uncatalyzed reaction TS-**K**. For example, the bond lengths and bond orders in the uncatalyzed reaction are 1.93 Å and 0.37 for the O1–C5 bond and 2.47 Å and 0.19 for the C3–C4 bond, while those in

the catalyzed reaction are 1.88 Å and 0.59 for the O1–C5 bond and 2.94 Å and 0.05 for the C3–C4 bond. Apparently, the asynchronism in the bond formation of O1–C5 precedes to that of C3–C4 in the transition state of the catalyzed reaction.



TS **J** (catalyzed)

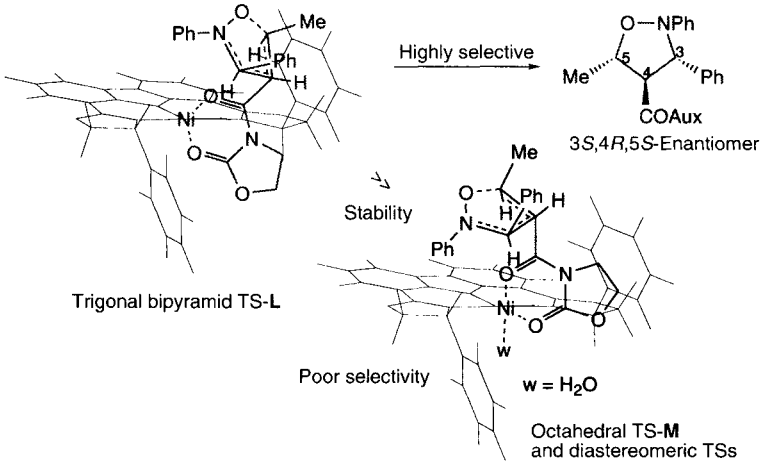
O1 - N2	1.39 Å	0.94
N2 - C3	1.26	1.42
C3 - C4	2.94	0.05
C4 - C5	1.39	1.04
C5 - O1	1.88	0.59
C4 - C6	1.39	1.43
C6 - O7	1.26	1.19
O7 - B8	1.62	0.56

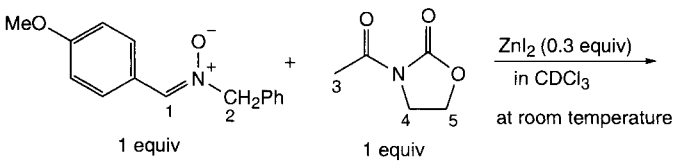
TS **K** (uncatalyzed)

O1 - N2	1.37 Å	1.02
N2 - C3	1.28	1.34
C3 - C4	2.47	0.19
C4 - C5	1.37	1.38
C5 - O1	1.93	0.37
C4 - C6	1.45	0.99
C6 - O7	1.22	1.73

Scheme 7.30

The simple structure of *R,R*-DBFOX/Ph complex catalysts facilitates discussion of transition structures and proceeds insight into the role of MS 4 Å. On the basis of ab-initio molecular orbital calculations of a model nitrone cycloaddition, a variable temperature ^{1}H NMR study of the substrate complex derived from DBFOX/Ph, $Zn(ClO_4)_2$, 3-acetyl-2-oxazolidinone, and the observed high catalytic activity, the nitrone cycloaddition in the presence of MS 4 Å is most likely to proceed through the transition structure TS-**L** with a trigonal bipyramid structure (Scheme 7.31). Face shielding by one of the 4-phenyl substituents (the top 4-phenyl) becomes very effective and the other 4-phenyl substituent (the bottom 4-phenyl) inhibits the *exo* approach of the nitrone. As a result, the reaction shows high *endo*- and enantioselectivities in the absence of water. In the reactions catalyzed by the aqua DBFOX complex in the absence of MS 4 Å, a water molecule coordinates on the nickel ion so that octahedral transition structure TS-**M** becomes predominant. The reaction site of the coordinated substrate in TS-**M** is more open for the approach of nitrone, and both the *si* and *re* faces (C*β*) allow the attack of nitrone, showing low enantioselectivity. In addition, the *exo* approach of nitrone leading to 3,4-*cis* isoxazolidines is not difficult, and poor *endo* selectivity results. Even when a trace of water is present, TS-**L** may participate predominantly to the reaction since the octahedral complex catalyst should be less reactive than the trigonal bipyramid complex catalyst based on the *trans* effect by the aqua ligand.





	Nitrone		Dipolarophile		
	H-1^s	H-2^s	H-3^s	H-4^t	H-5^t
Without LA	7.31	5.01	2.53	4.02	4.41
With ZnI_2	7.40	5.19	2.52	4.00	4.40
Shifts Δδ	0.09	0.18	-0.01	-0.02	-0.01

1. LA predominantly coordinates to the nitrone rather than the chelating dipolarophile.
2. The free nitrone is rapidly exchanging with the complexed one.
3. Cycloaddition proceeds through the dipolarophile/LA complex.

Scheme 7.31

7.4 Diazo Cycloadditions

No single examples have been reported so far for the catalyzed asymmetric diazoalkane cycloadditions. Based on the kinetic data on the relative reaction rates observed by Huisgen in the competitive diazomethane cycloadditions between 1-alkene and acrylic ester (Scheme 7.32), it is found that diazomethane is most nucleophilic of all the 1,3-dipoles examined ($k_{\text{acrylate}}/k_{\text{1-alkene}} = 250\,000$) [78]. Accordingly, the cycloadditions of diazoalkanes to electron-deficient alkenes must be most efficient when catalyzed by a Lewis acid catalyst. The author's group has become aware of this possibility and started to study the catalyzed enantioselective diazoalkane cycloadditions of 3-(2-alkenoyl)-2-oxazolidinones.

Diazoalkane cycloadditions to alkenes produce 1-pyrazolines as the initial cycloadducts which are not so quite stable that these undergo spontaneous 1,3-proton

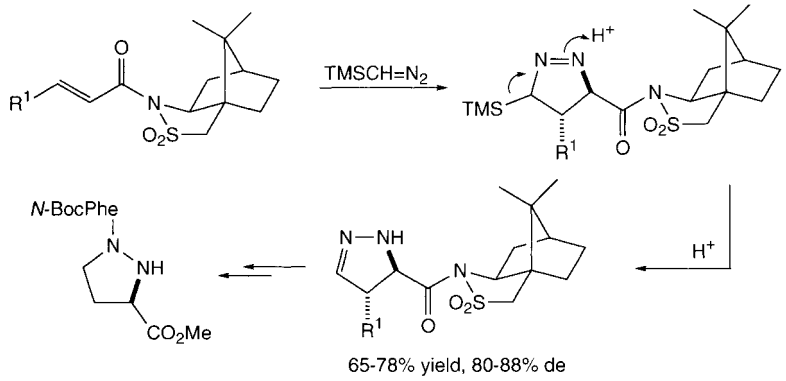
Relative Cycloaddition Rates

1,3-Dipole	Acrylic ester	1-Alkene	Vinyl ether	Enamine
Diazomethane	250,000	1	0.02	0.07[a]
Diphenyldiazomethane	13,500	1		
Diazoacetic ester	930	1	0.1	470[a]
Diazomalonic ester	35	1	0.15	620[a]
Phenyl azide	41	1	1.7	500,000[a]
Diphenylnitrilimine	350	1	2.3	41[b]
Benzonitrile oxide	25	1	7	81[b]
Phenylsulfonylnitrile oxide	1	1	13	
Azomethine imine	55	1	12	
C-Merthyl-N-phenylsydnone	15	1		
C-Phenyl-N-methylnitrone	150	1		

[a]1-Pyrrolidinocyclopentene, [b]β-Pyrrolidinostyrene

Scheme 7.32

migration leading to thermodynamically more stable 2-pyrazoline derivatives [79]. Usually a more acidic hydrogen moves and consequently the chirality at this position disappears. Carreira and co-workers have recently reported the diastereoselective diazoalkane cycloadditions of trimethylsilyldiazomethane to chiral alkenes [80]. Upon treatment with a protonic acid or acid chloride-silver triflate after the completion of reaction, the 1-pyrazolines as the initial cycloadducts underwent a regioselective protodesilylation or acyldesilylation of the 2,3-diazoallylsilane moiety masked in the resulting heterocycles to produce 2-pyrazolines (Scheme 7.33).



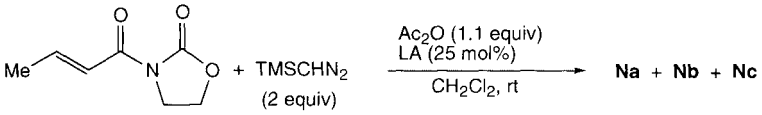
M. R. Mish, F. M. Guerra, and E. M. Carreira, *J. Am. Chem. Soc.*, 1997, 119, 8379-8380.

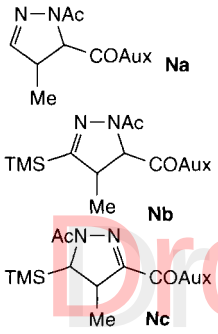
Scheme 7.33

7.4.1
Screening of Lewis Acid Catalysts

Accordingly, we examined the cycloaddition reactions using trimethylsilyldiazomethane and 3-crotonoyl-2-oxazolidinone in the presence of a wide variety of Lewis

acid catalysts (25 mol%) in dichloromethane at room temperature [81]. Acetic anhydride was used for the electrophile to induce the regioselective desilylation. As shown in the table of Scheme 7.34, some Lewis acid catalysts showed significant rate acceleration, titanium and ytterbium salts being especially effective. Three kinds of 2-pyrazoline cycloadducts, **Na**, **Nb**, and **Nc**, were produced together with other products in some cases, and the product ratios depended upon the nature of Lewis acid catalysts employed. Types of products were presumably determined depending upon the difference of coordination types of the catalyst (Scheme 7.34).

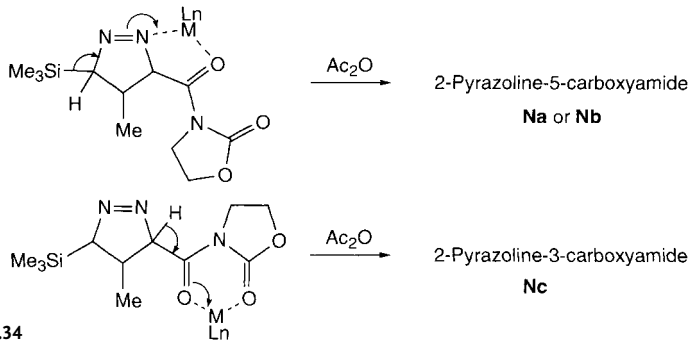




Aux: 2-oxo-3-oxazolidinyl

Lewis acid	Time/h	Yield/% Na	Nb	Nc	Recovered
-	6 d	14	2	84	0
$MgBr_2$	4.5	34	27	22	0
$MnBr_2$	10	44	7	17	15
$FeCl_2$	10	19	23	41	13
$CoBr_2$	10	14	6	40	45
$NiBr_2$	10	24	+	69	6
ZnI_2	4.5	63	12	0	0
$SnCl_2$[a]	10	6	0	16	16
$SnCl_4$[a]	10	+	0	12	12
$Ti(OPr\text{-}i)_4$	10	30	+	11	10
$Yb(OTf)_3$[b]	0.5	20	+	+	0
$TiCl_2(OPr\text{-}i)_2$	0.5	59	9	0	0

[a]Four unidentified products were obtained. [b]The major product: unidentified.

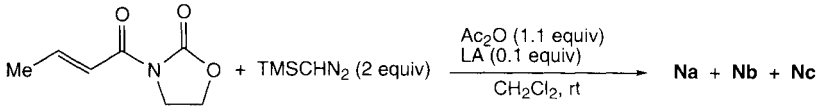


Scheme 7.34

When the catalyst coordinates to the pyrazoline nitrogen and carbonyl oxygen at the step of 1-pyrazoline formation, desilylation or deprotonation takes place at the same position to give either **Na** or **Nb**, respectively. On the other hand, when the catalyst coordinates to the two carbonyl oxygens, the methine hydrogen derived from the acceptor molecule is deprotonated to give **Nc**. In the reaction using a Le-

wis acid catalyst which is rather insoluble in the reaction solvent, the more acidic methine hydrogen migrates to give **Nc**.

It was our delight that the reactions catalyzed were activated even at –40 °C in the presence of a catalytic amount of achiral titanium catalysts (10 mol%) to afford the desilylacetylated 2-pyrazoline cycloadduct **Na**, 1-acetyl-4-methyl-5-(2-oxo-3-oxazolidinylcarbonyl)-2-pyrazoline, in high yields as the far major product (Scheme 7.35). Although some chiral titanium TADDOlate catalysts were successfully applied to activate these reactions leading to the moderate enantioselectivities (up to 55% ee), the chemical yields were not satisfactory.



Catalyst/10 mol%	Temp/°C	Time/h	Yield/% Na	Nb	Nc	% ee
$TiBr_2(OPr\text{-}i)_2$	-40	48	69	5	+	-
$TiBr_2(OPr\text{-}i)_2$/MS 4A	-40	48	82	5	+	-
TADDOL/Ph/$TiBr_2(OPr\text{-}i)_2$	-40	72	72	10	8	-37
TADDOL/1-Np/$TiBr_2(OPr\text{-}i)_2$	-40	72	17	+	+	45
TADDOL/2-Np/$TiBr_2(OPr\text{-}i)_2$	-40	72	17	+	+	-55
TADDOL/Ph/$TiBr_2(OPr\text{-}i)_2$/MS 4A	-40	24	63	0	2	-23
TADDOL/Ph/$TiBr_2(OPr\text{-}i)_2$/MS 4A	-40	24	58	24	19	-19*

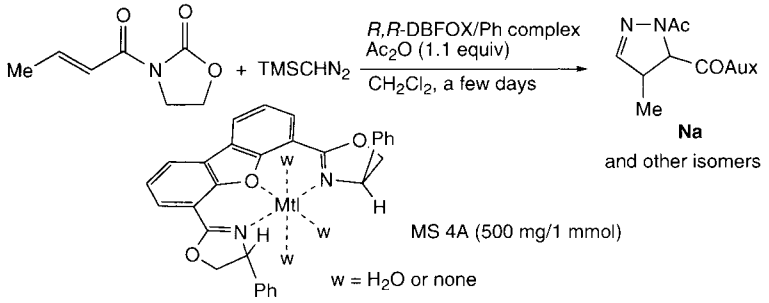
MS 4A (500 mg/1 mmol). *3-Acryloyl-2-oxazolidinone

Scheme 7.35

7.4.2
Zinc Complex-catalyzed Asymmetric Reactions

After screening of several of other chiral catalysts, the nickel(II) and zinc(II) complexes of *R,R*-DBFOX/Ph ligand were found to be reactive even when they were used in catalytic amounts (10 mol%) in dichloromethane. A high chemical yield of the desilylacetylated 2-pyrazoline cycloadduct **Na** was obtained as the single product, and the zinc(II) complex was found to be the best catalyst [81]. Thus, the maximum enantioselectivity as high as 99% ee was attained in the reaction catalyzed by *R,R*-DBFOX/Ph·$Zn(ClO_4)_2 \cdot 3H_2O$ (10 mol%) at –40 °C among a little excess of trimethylsilyldiazomethane (1.2 equiv.), 3-crotonoyl-2-oxazolidinone, acetic anhydride (1.1 equiv.), and MS 4 Å (Scheme 7.36). The presence of MS 4 Å was essential because no formation of any cycloadducts was observed without MS 4 Å, the starting trimethylsilyldiazomethane being recovered intact. The role of MS 4 Å is simply a dehydrating agent in this case since the comparable results were obtained in the reaction catalyzed by the anhydrous complex catalyst prepared from *R,R*-DBFOX/Ph, ZnI_2, and $AgClO_4$.

Unfortunately the reaction of trimethylsilyldiazomethane with 2-acryloyl-2-oxazolidinone led to a racemic result. Since 2-acryloyl-2-oxazolidinone has a terminal-



Metal salt (mol%)	Temp/°C	TMSCH=N_2/equiv	**Na**	% ee
$Zn(ClO_4)_2 \cdot 6H_2O$ (10)	rt	2	49%	40
$Zn(ClO_4)_2 \cdot 6H_2O$ (10)	-20	2	85	92
$Zn(ClO_4)_2 \cdot 6H_2O$ (10)	-40	2	85	96
$Zn(ClO_4)_2$ (10)	-40	2	81	97
$Zn(ClO_4)_2 \cdot 6H_2O$ (10)	-40	1.2	87	99
$Zn(ClO_4)_2 \cdot 6H_2O$ (5)	-40	1.2	79	96
$Mg(ClO_4)_2$ (10)	rt	2	61	64
$Mg(ClO_4)_2$ (10)	-20	2	64	82
$Mg(ClO_4)_2$ (10)	-40	2	75	37
$Ni(ClO_4)_2 \cdot 6H_2O$ (10)	-40	2	79	93
$Cu(ClO_4)_2 \cdot 6H_2O$ (10)	0	2	+	-

Scheme 7.36

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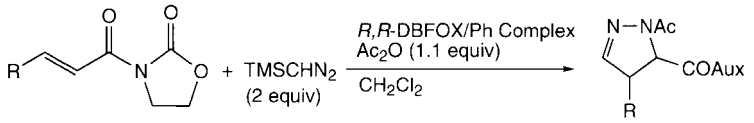
ly unsubstituted reaction site, its reaction presumably proceeded through a different reaction mechanism, either the *endo* approach of trimethylsilyldiazomethane or stepwise linear approach. Surprisingly, both the 3-acryloyl-2-oxazolidinones bearing propyl and isopropyl substituents at the *β*-position were much less enantioselective than the methyl-substituted dipolarophile (Scheme 7.37). Especially, the reaction of 3-(2-hexenoyl)-2-oxazolidinone as the primary alkyl-substituted dipolarophile never exceeded an enantioselectivity of 50% ee. These *β*-substituents, isopropyl and propyl moieties, have higher mobility than the methyl substituent, and therefore, some serious steric hindrance should exist against one of the shielding phenyl groups so that the reaction site departs from the shielding phenyl group. As a result, efficiency of the chiral shielding became rather ineffective.

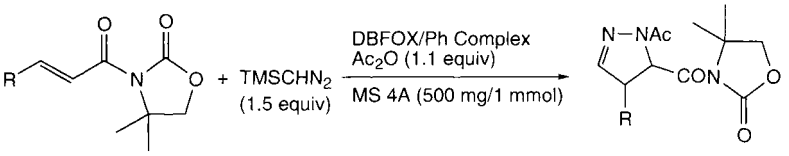
On the other hand, use of 4,4-dimethyl-2-oxazolidinone as chiral auxiliary was very effective. It was found that the *R,R*-DBFOX/Ph·$Mg(ClO_4)_2$ complex was the catalyst of choice to mediate the reactions with 3-crotonoyl-4,4-dimethyl-2-oxazolidinone, because both the *R,R*-DBFOX/Ph-zinc(II) and –nickel(II) complexes were totally inactive. Thus, the *R,R*-DBFOX/Ph·$Mg(ClO_4)_2$-catalyzed reaction of trimethylsilyldiazomethane with 3-crotonoyl-4,4-dimethyl-2-oxazolidinone in the presence of MS 4 Å proceeded smoothly even at –78 °C to give the corresponding cycloadduct in 75% yield with the enantioselectivity of 97% ee. Other dipolarophiles such as the 4,4-dimethyl-2-oxazolidinones having 2-hexenoyl and 4-methyl-2-pentenoyl substituents at the nitrogen atom of the oxazolidinone-chelating auxiliary showed similarly high enantioselectivities of 98% ee regardless of the *β*-substituents of dipolarophiles (Scheme 7.38).



and other isomers

R	Metal salt (mol%)	Temp/°C	Time/h	Yield of A/%	% ee
H	$Zn(ClO_4)_2 \cdot 6H_2O$ (10)	-78	40	79	0
i-Pr	$Zn(ClO_4)_2 \cdot 6H_2O$ (10)	-40	22	89	71
n-Pr	$Zn(ClO_4)_2 \cdot 6H_2O$ (10)	-40	22	84	49
n-Pr	$Zn(ClO_4)_2 \cdot 6H_2O$ (10)	-55	48	81	50
n-Pr	$Ni(ClO_4)_2 \cdot 6H_2O$ (10)	-40	22	43	47

Scheme 7.37



R	Metal salt (mol%)	Temp/°C	Time/h	Yield of **Na**/%	% ee
Me	$Mg(ClO_4)_2$ (10)	-40	24	71	89
Me*	$Mg(ClO_4)_2$ (10)	-40	24	63	82
Me	$Mg(ClO_4)_2$ (10)	-78	24	75	97
n-Pr	$Mg(ClO_4)_2$ (10)	-60	48	62	98
i-Pr	$Mg(ClO_4)_2$ (10)	-60	48	93	98
t-Bu	$Mg(ClO_4)_2$ (10)	rt	24	0	
EtOOC	$Mg(ClO_4)_2$ (10)	-78	4	61	-**

*In the absence of MS 4A. **$[\alpha]_D^{23}$ = 30.09 (c = 1.10, $CHCl_3$)

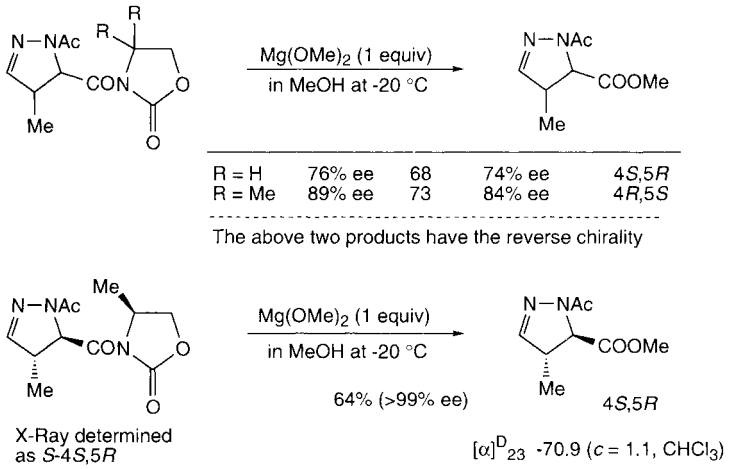
In the above reactions the magnesium complex is specifically active catalyst. Neither *R,R*-DBFOX/Ph•$Zn(ClO_4)_2 \cdot 3H_2O$ (10) nor *R,R*-DBFOX/Ph•$Ni(ClO_4)_2 \cdot 3H_2O$ (10) shows any catalytic activity.

Scheme 7.38

7.4.3 Transition Structures

The desilylacetylated cycloadducts, produced from the reactions of trimethylsilyldiazomethane with 3-crotonoyl-2-oxazolidinone or 3-crotonoyl-4,4-dimethyl-2-oxazolidinone, were transformed to methyl *trans*-1-acetyl-4-methyl-1-pyrazoline-5-carboxylate through the reactions with dimethoxymagnesium at –20 °C. When the optical rotations and chiral HPLC data were compared between these two esters, it was found that these two products had opposite absolute stereochemistry (Scheme 7.39). The absolute configuration was identified on the basis of the X-ray-determined structure of the major diastereomer of cycloadduct derived from the reaction of trimethylsilyldiazomethane to (*S*)-3-crotonoyl-4-methyl-2-oxazolidinone.

The cycloaddition product derived from 3-crotonoyl-2-oxazolidinone was identified to be the 4*S*,5*R*-enantiomer of 2-pyrazoline cycloadduct, meaning that the *re,si*-enan-



Scheme 7.39

tioface of the dipolarophile was involved in the attack of trimethylsilyldiazomethane as a result of the chiral shielding from the top 4-phenyl substituent, as shown in the trigonal bipyramid transition structure TS-**O** (Scheme 7.40). The selected enantioface of 3-crotonoyl-2-oxazolidinone was the same to that involved in the transition structure of the *R,R*-DBFOX/Ph·Ni$(ClO_4)_2 \cdot 3H_2O$-catalyzed Diels-Alder reaction using cyclopentadiene and the same dienophile [39]. Consequently, the absolute configuration of the cycloaddition product produced in the diazo cycloaddition reaction of 3-crotonoyl-4,4-dimethyl-2-oxazolidinone was the 4*R*,5*S* enantiomer which resulted from the selection of *si,re*-enantioface of the oxazolidinone dipolarophile. The twisted trigonal bipyramid type transition structure TS-**P** is most likely to be involved if this dipolarophile has worked as bidentate dipolarophile in the reaction, in which the absolute configuration of the cycloadduct was induced from the chiral shielding by the opposite phenyl shielding substituent (the bottom 4-phenyl).

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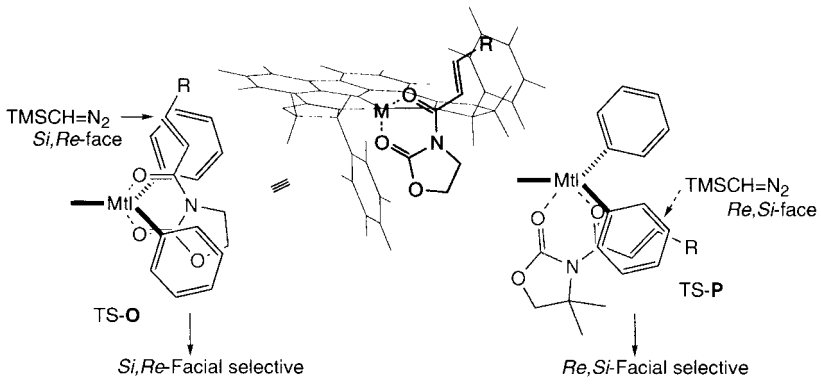


Scheme 7.40

However, we have so far no satisfactory explanation for the phenomenon that the reaction was selectively activated only by the magnesium complex catalyst. Since two methyl substituents exist at the 4-position of oxazolidinone-chelating auxiliary, the both enantiofaces of the reacting substrate complex should be sterically hindered. This is no doubt the major reason for the failure of activation by the nickel(II) and zinc(II) complex catalysts in the trigonal bipyramid transition structure like TS-**O**. The *R,R*-DBFOX/Ph-magnesium complex was apparently not much better catalyst in the reactions of trimethylsilyldiazomethane with 3-crotonoyl-2-oxazolidinone, so the reaction through the trigonal bipyramid transition structure, than the corresponding zinc(II) and nickel(II) catalysts. Therefore, one possibility would be the magnesium complex is especially an active catalyst in the twisted trigonal bipyramid transition structure. Activation through the single point coordination of dipolarophile also remains as a possibility.

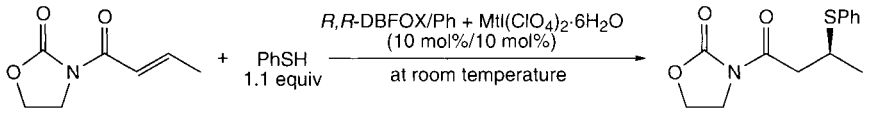
7.5 Conjugate Additions

One of the remarkable features of the *R,R*-DBFOX/Ph-transition metal aqua complexes is not only high enantioselectivity in the reactions catalyzed by the complexes but also high stability and tolerance toward nucleophilic or coordinating reagents. Therefore, these aqua complexes can be utilized as tolerant chiral Lewis acid catalysts in the catalyzed enantioselective reactions using highly coordinating nucleophiles, which are otherwise difficult to achieve [39, 82]. Probably the water ligands are rapidly exchanged with the acceptor and donor molecules, and this rapid ligand exchange reaction should be responsible for the high catalytic activity of these aqua complexes [57]. The aforementioned successful applications to the catalyzed enantioselective 1,3-dipolar cycloaddition reactions of nitrones [68, 76], cyclic nitronates [75], and diazoalkanes [81] are the examples. Accordingly, we further investigated the Lewis acid-catalyzed conjugate addition reactions using thiols [83], hydroxylamines, and carbon nucleophiles in the presence of amine bases.

7.5.1 Thiol Conjugate Additions

Quite a number of asymmetric thiol conjugate addition reactions are known [84], but previous examples of enantioselective thiol conjugate additions were based on the activation of thiol nucleophiles by use of chiral base catalysts such as amino alcohols [85], the lithium thiolate complex of amino bisether [86], and a lanthanide tris(binaphthoxide) [87]. No examples have been reported for the enantioselective thiol conjugate additions through the activation of acceptors by the aid of chiral Lewis acid catalysts. We therefore focussed on the potential of *R,R*-DBFOX/Ph aqua complex catalysts as highly tolerant chiral Lewis acid catalyst in thiol conjugate addition reactions.

Among a variety of DBFOX/Ph complexes examined as chiral catalysts in thiol conjugate addition reactions between thiophenol and 3-crotonoyl-2-oxazolidinone, the nickel(II) aqua complex *R,R*-DBFOX/Ph·$Ni(ClO_4)_2 \cdot 3H_2O$ was exceptionally effective (Scheme 7.41) [83]. Although the magnesium and zinc complexes prepared from *R,R*-DBFOX/Ph ligand by treatment with $Mg(ClO_4)_2$, $Zn(ClO_4)_2 \cdot 6H_2O$, $Zn(OTf)_2$, or ZnI_2 showed satisfactory catalytic activity, the enantioselectivities observed in the catalyzed thiol conjugate additions were relatively poor. On the other hand, metal complexes prepared from the perchlorates of copper(II), iron(II), and manganese(II) ions showed only a low catalytic activity. Accordingly, reactions of a variety of thiols were catalyzed by the aqua nickel(II) complex *R,R*-DBFOX/Ph·$Ni(ClO_4)_2 \cdot 3H_2O$ to give the corresponding adducts. Satisfactorily high enantioselectivities as well as high chemical yields were observed with some exceptions when the reactions were performed in THF at room temperature. Based on the absolute configuration of the thiophenol adduct, it was found that the thiol conjugate addition took place on the *si* face of the 3-crotonoyl-2-oxazolidinone.

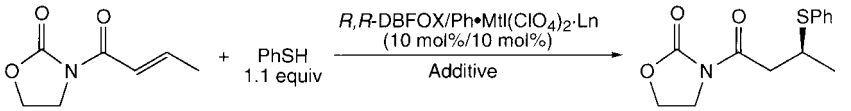


Metal Salt	Solvent	Time/h	Yield/%	ee%[a]
$Mg(ClO_4)_2$	CH_2Cl_2	24	quant	52
$Mn(ClO_4)_2 \cdot 6H_2O$[b]	THF	24	quant	25
$FeCl_2$+2$AgClO_4$	THF	24	7	0
$Cu(ClO_4)_2 \cdot 6H_2O$	THF	24	49	-11
$Zn(ClO_4)_2 \cdot 6H_2O$	THF	24	62	0
$Ni(ClO_4)_2 \cdot 6H_2O$	THF	48	quant	80

[a] Determined by HPLC (Daicel Chiral Cel OD-H). [b] *R,R*-DBFOX/Ph was added to a mixture of $Ni(ClO_4)_2 \cdot 6H_2O$, thiophenol, and 3-crotonoyl-2-oxazolidinone.

Scheme 7.41

Enantioselectivities were found to change sharply depending upon the reaction conditions including catalyst structure, reaction temperature, solvent, and additives. Some representative examples of such selectivity dependence are listed in Scheme 7.42. The thiol adduct was formed with 79% ee (81% yield) when the reaction was catalyzed by the *R,R*-DBFOX/Ph aqua nickel(II) complex at room temperature in dichloromethane. Reactions using either the anhydrous complex or the aqua complex with MS 4 Å gave a racemic adduct, however, indicating that the aqua complex should be more favored than the anhydrous complex in thiol conjugate additions. Slow addition of thiophenol to the dichloromethane solution of 3-crotonoyl-2-oxazolidinone was ineffective for enantioselectivity. Enantioselectivity was dramatically lowered and reversed to –17% ee in the reaction at –78 °C. A similar tendency was observed in the reactions in diethyl ether and THF. For example, a satisfactory enantioselectivity (80% ee) was observed in the reaction in THF at room temperature, while the selectivity almost disappeared (7% ee) at 0 °C.



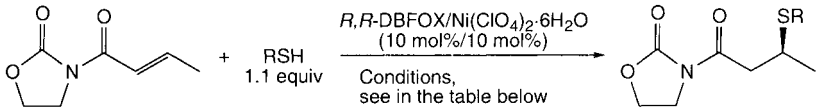
Metal Salt	Solvent	Temp/°C	Time/h	Yield/%	ee/%[a]
$Ni(ClO_4)_2{\cdot}6H_2O$[b]	CH_2Cl_2	rt	48	81	79
$NiBr_2 + AgClO_4$ (2 equiv)	CH_2Cl_2	rt	72	50	0
$Ni(ClO_4)_2{\cdot}6H_2O$[c]	CH_2Cl_2	rt	24	91	20
$Ni(ClO_4)_2{\cdot}6H_2O$[b]	CH_2Cl_2	78	48	33	-17
$NiBr_2 + AgClO_4$ (2 equiv)	Et_2O	rt	48	50	-10
$Ni(ClO_4)_2{\cdot}6H_2O$	Et_2O	rt	24	42	73
$Ni(ClO_4)_2{\cdot}6H_2O$	THF	rt	24	quant	80
$Ni(ClO_4)_2{\cdot}6H_2O$	THF	0	72	62	7
$Ni(ClO_4)_2{\cdot}6H_2O$	CH_2Cl_2/MeOH = 1/1 v/v	rt	24	quant	82
$Ni(ClO_4)_2{\cdot}6H_2O$	CH_2Cl_2/AcOH = 10/1 v/v	rt	48	99	0
$Ni(ClO_4)_2{\cdot}6H_2O$	CH_2Cl_2/sat. NH_4Cl aq. = 10/1 v/v	rt	48	99	-27

[a] Determined by HPLC (Daicel Chiral Cel OD-H). [b] *R,R*-DBFOX/Ph was added to the mixture of $Ni(ClO_4)_2{\cdot}6H_2O$, thiophenol and 3-crotonoyl-2-oxazolidinone. [c] Thiophenol was added slowly to a mixture of the catalyst and 3-crotonol-2-oxazolidinone in a period of 3 h.

Scheme 7.42

To examine such high sensitivity of enantioselectivity to the reaction conditions, the reactions of thiophenol with 3-crotonoyl-2-oxazolidinone were performed in dichloromethane at room temperature in the presence of a variety of additives. Although addition of methanol (CH_2Cl_2–MeOH = 10:1 *v*/*v*) did not affect either the chemical yield or enantioselectivity (quant, 82% ee), addition of acetonitrile or *N,N*-dimethylformamide (both 1:1 *v*/*v* ratios) slowed the reactions (13%, 15% yields) and provided products with lower enantioselectivities (19%, 30% ee). The presence of acetic acid, even in a small amount (CH_2Cl_2–AcOH = 10:1 *v*/*v*), gave the racemic product, while saturated aqueous ammonium chloride provided a reversed enantioselectivity (CH_2Cl_2–sat. NH_4Cl aq. = 10:1 *v*/*v*, 99% yield, –27% ee). To our delight, however, reaction in the mixed solvent CH_2Cl_2–THF = 10:1 *v*/*v* catalyzed by the *R,R*-DBFOX/Ph aqua nickel(II) complex at 0 °C in the presence of *N,N,N′,N′*-tetramethyl-1,8-diaminonaphthalene (proton sponge, 10 mol%) gave the best result (84% yield, 94% ee). Some other thiols provided excellent enantioselectivities under similar reaction conditions with 97% ee for a bulky thiol such as *o*-isopropylbenzenethiol (Scheme 7.43).

At the beginning of the work, it was suspected that thiols would strongly coordinate to the Lewis acid catalyst to poison its catalytic activity even if the *R,R*-DBFOX/Ph·$Ni(ClO_4)_2 \cdot 3H_2O$ catalyst is tolerant. We therefore examined the interaction between thiophenol and the catalyst *R,R*-DBFOX/Ph·$Ni(ClO_4)_2 \cdot 3H_2O$ to learn about the catalytic activity of the thiol-coordinating complex. When thiophenol was added to the solution of *R,R*-DBFOX/Ph·$Ni(ClO_4)_2 \cdot 3H_2O$ in THF, the original pale blue color of the catalyst gradually faded to reddish brown. This color change was rapid in dichloromethane, probably arising from the coordination of thiol to the catalyst. A brown colored solid was isolated as precipitate on treatment with a mixture of isopropyl alcohol and hexane, and this solid was



R	Time/h	Yield/%	ee%
Phenyl	24	84	94
o-Tolyl	96	99	95
p-Tolyl	96	84	91
Mesityl	96	36	96
o-Isopropylphenyl	96	91	97
o-*tert*-Butylphenyl	96	96	94
p-*tert*-Butylphenyl	96	38	69
1-Naphthyl	96	92	55
2-Naphthyl	96	88	91

Reaction conditions:
1. 3-Crotonoyl-2-oxazolidinone 1.0 equiv
2. RSH 1.1 equiv
3. (*R*,*R*)-DBFOX/Ph 0.1 equiv
4. $Ni(ClO_4)_2 \cdot 6H_2O$ 0.1 equiv
5. Proton Sponge 0.1 equiv
6. At 0 °C in CH_2Cl_2/THF = 10/1 v/v
7. Under N_2

Proton Sponge: *N*,*N*,*N*′,*N*′-Tetramethyl-1,8-diaminonaphthalene

Scheme 7.43

found to show sufficient catalytic activity in the reaction leading to a high enantioselectivity (97% yield, 70% ee). Accordingly, it seems likely that the thiol certainly binds with the catalyst, but the binding is not so strong that the thiol ligand may be easily replaced with the acceptor molecule in the reaction. This ligand exchange should be more favored in a coordinating media such as THF. However at the same time, THF competes with the acceptor molecule in coordination to the catalyst to deactivate the reaction. In the presence of an amine base such as pyridine or triethylamine, a totally inert reddish brown complex immediately precipitated. Since the resulting brown solid is totally insoluble in the reaction medium and free from perchlorate ions (according to analysis for chloride), we assume that the perchlorate counter-ions have been replaced with the highly nucleophilic thiolate ions.

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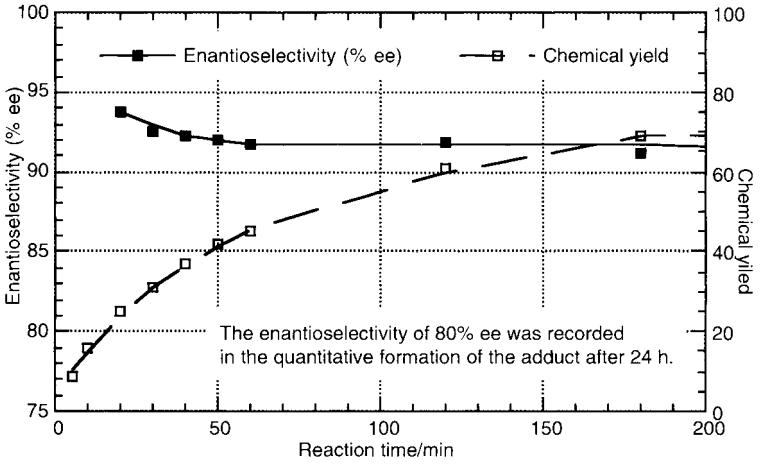
The time-dependence of enantioselectivity in the reaction thiophenol with 3-crotonoyl-2-oxazolidinone catalyzed by *R*,*R*-DBFOX/Ph·$Ni(ClO_4)_2 \cdot 3H_2O$ at room temperature in THF is shown in Scheme 7.44. After 3 h, the yield of the thiol adduct is 70% with the enantioselectivity of 91% ee, but the enantioselectivity was 80% ee at the completion of reaction after 24 h (yield 100%). Although the catalyst maintains a high catalytic activity, and hence a satisfactory enantioselectivity, at the early stage of reaction, the deterioration of catalyst cannot be neglected thereafter even under neutral conditions.

7.5.2
Hydroxylamine Conjugate Additions

With the success in Lewis acid-catalyzed thiol conjugate addition reactions mentioned above, we further tried to apply the *R*,*R*-DBFOX/Ph-nickel(II) aqua complex catalyst to the catalyzed asymmetric conjugate addition reactions of hydroxylamines [88, 89]. However, after some preliminary examinations, we found that



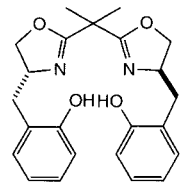
Scheme 7.44

these catalysts were totally ineffective in the reactions of *O*-benzylhydroxylamine and *N*-benzylhydroxylamine with 3-(2-alkenoyl)-2-oxazolidinones. Both rate acceleration and enantioselectivities were disappointingly low.

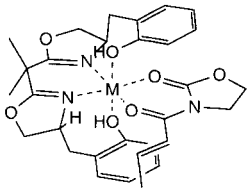
We therefore prepared a new chiral ligand, (*R,R*)-isopropylidene-2,2′-bis[4-(*o*-hydroxybenzyl)oxazoline)], hereafter designated *R,R*-BOX/*o*-HOBn. To our delight, the copper(II) complex catalyst prepared from *R,R*-BOX/*o*-HOBn ligand and $Cu(OTf)_2$ was quite effective (Scheme 7.45). Especially, the reaction of *O*-benzylhydroxylamine with 1-crotonoyl-3-isopropyl-2-imidazolidinone in dichloromethane (0.15 M) at –40 °C in the presence of *R,R*-BOX/*o*-HOBn · $Cu(OTf)_2$ (10 mol%) provided the maximum enantioselectivity of 94% ee.

The importance of the *o*-hydroxyl moiety of the 4-benzyl-shielding group of *R,R*-BOX/*o*-HOBn · $Cu(OTf)_2$ complex was indicated when enantioselectivities were compared between the following two reactions. Thus, the enantioselectivity observed in the reaction of *O*-benzylhydroxylamine with 1-crotonoyl-3-phenyl-2-imidazolidinone catalyzed by this catalyst was 85% ee, while that observed in a similar reaction catalyzed by *R,R*-BOX/Bn.$Cu(OTf)_2$ having no hydroxyl moiety was much lower (71% ee). In these reactions, the same mode of chirality was induced (Scheme 7.46). We believe the free hydroxyl groups can weakly coordinate to the copper(II) ion to hinder the free rotation of the benzyl-shielding substituent across the C(4)–CH_2 bond. This conformational lock would either make the coordination of acceptor molecules to the metallic center of catalyst easy or increase the efficiency of chiral shielding of the coordinated acceptor molecules.

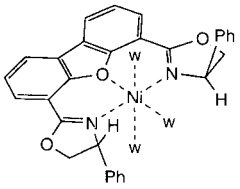
1-Alkyl-2-imidazolidinones-chelating auxiliaries are more electron donating than 1-phenyl-2-imidazolidinone and 2-oxazolidinone auxiliaries so that the unsaturated amides of 1-alkyl-2-imidazolidinones should be less reactive under uncatalyzed conditions than those of 3-phenyl-2-imidazolidinone and 2-oxazolidinone. On the other hand, the coordinating ability to the catalyst is increased to be activated. Accordingly, the reaction rate difference between the catalyzed and uncatalyzed reac-



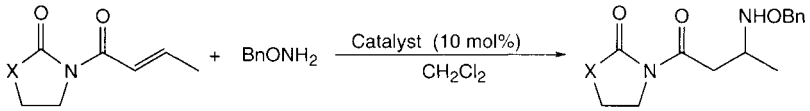
R,R-BOX/*o*-HOBn



Possible structure for the substrate complex



R,R-DBFOX/Ph•Ni$(ClO_4)_2$•3H_2O



X	Catalyst	Temp / °C	Time / h	Yield /%	% *ee*[a]
O	*R,R*-DBFOX/Ph·Ni$(ClO_4)_2$	rt	18	71	29
PhN	*R,R*-DBFOX/Ph·Ni$(ClO_4)_2$	rt	114	61	51
O	*R,R*-BOX/*o*-HOBn·Cu$(OTf)_2$	-20	166	44	11
PhN	*R,R*-BOX/*o*-HOBn·Cu$(OTf)_2$	rt	3	71	85
PhN	*R,R*-BOX/*o*-HOBn·Cu$(OTf)_2$	-20	40	77	89
MeN	*R,R*-BOX/*o*-HOBn·Cu$(OTf)_2$	rt	1	77	89
MeN	*R,R*-BOX/*o*-HOBn·Cu$(OTf)_2$	-20	28	25	91
i-PrN	*R,R*-BOX/*o*-HOBn·Cu$(OTf)_2$	-20	5	83	92
i-PrN	*R,R*-BOX/*o*-HOBn·Cu$(OTf)_2$	-40	93	59	94

[a]Determined by chiral column HPLC.

Scheme 7.45

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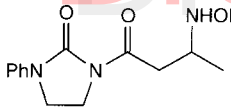
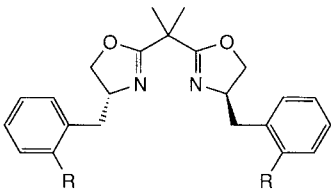
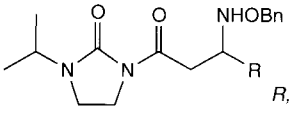


R,R-BOX/Bn•Cu$(OTf)_2$ (10 mol%): rt, 2 h, 70% (71% ee)

R,R-BOX/*o*-HOBn•Cu$(OTf)_2$ (10 mol%): rt, 3 h, 71% (85% ee)



R = H: *R,R*-BOX/Bn
R = OH: *R,R*-BOX/*o*-HOBn



R,R-BOX/*o*-HOBn•Cu$(OTf)_2$ (10 mol%)

R	Temp/°C	Time/h	Yield/%	ee %
Et	-20	71	60	91
i-Pr	-20	63	38	94
t-Bu	rt	17	72	80

Scheme 7.46

tions should be greater in the case of derivatives of 1-alkyl-2-imidazolidinones. Competitive coordination of substrates, this case *O*-benzylhydroxylamine and acceptors, affects the total reaction rate in the Lewis acid-catalyzed reactions using

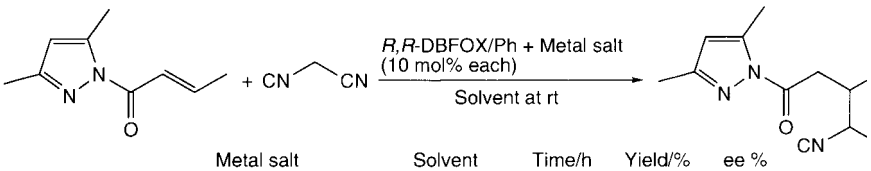
coordinating nucleophiles so that the imidazolidinone acceptors are much more effective in reactivities and enantioselectivities as shown in the table of Scheme 7.45.

Several derivatives of 1-(2-alkenoyl)-3-isopropyl-2-imidazolidinones having ethyl, isopropyl, and *t*-butyl *β*-substituents can be successfully applied to give satisfactory enantioselectivities (Scheme 7.46).

7.5.3
Michael Additions of Carbon Nucleophiles

The *R,R*-DBFOX/Ph-transition metal aqua complex catalysts should be suitable for the further applications to conjugate addition reactions of carbon nucleophiles [90–92]. What we challenged is the double activation method as a new methodology of catalyzed asymmetric reactions. Therein donor and acceptor molecules are both activated by achiral Lewis amines and chiral Lewis acids, respectively; the chiral Lewis acid catalysts used in this reaction are *R,R*-DBFOX/Ph-transition metal aqua complexes.

We employed malononitrile and 1-crotonoyl-3,5-dimethylpyrazole as donor and acceptor molecules, respectively. We have found that this reaction at room temperature in chloroform can be effectively catalyzed by the *R,R*-DBFOX/Ph-nickel(II) and -zinc(II) complexes in the absence of Lewis bases leading to 1-(4,4-dicyano-3-methylbutanoyl)-3,5-dimethylpyrazole in a good chemical yield and enantioselectivity (Scheme 7.47). However, copper(II), iron(II), and titanium complexes were not effective at all, either the catalytic activity or the enantioselectivity being not sufficient. With the *R,R*-DBFOX/Ph-nickel(II) aqua complex in hand as the most reactive catalyst, we then investigated the double activation method by using this catalyst.

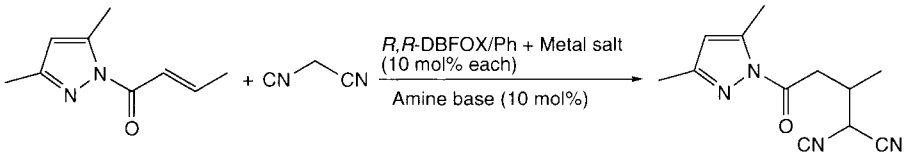


Metal salt	Solvent	Time/h	Yield/%	ee %
$Ni(ClO_4)_2 \cdot 6H_2O$	$CHCl_3$	24	92	84
$Zn(ClO_4)_2 \cdot 6H_2O$	$CHCl_3$	79	86	77
$Cu(ClO_4)_2 \cdot 6H_2O$	$CHCl_3$	24	12	2
$Ni(ClO_4)_2 \cdot 6H_2O$	CH_2Cl_2	24	57	51
$Ni(ClO_4)_2 \cdot 6H_2O$	THF	96	67	75
$Cu(ClO_4)_2 \cdot 6H_2O$	THF	63	2	27
$Fe(ClO_4)_2$	THF	54	6	40
$TiCl_2(OPr\text{-}i)_2O$	THF	24	trace	-

Scheme 7.47

A variety of amine bases were used in 10 mol%, equivalent amount to that of the *R,R*-DBFOX/Ph·$Ni(ClO_4)_2 \cdot 3H_2O$ catalyst, in the reaction between malononitrile and 1-crotonoyl-3,5-dimethylpyrazole in dichloromethane (Scheme 7.48). Not only

reactivities but also enantioselectivities were found to depend upon the nature of amine bases, reaction solvents, and reaction temperatures. Reaction rates were extremely decreased at a low temperature, and enantioselectivities were not always higher in the reactions done at a lower temperature. One typical example is the reaction using triethylamine as base catalyst, where the racemic adduct was formed in 83% yield at –40 °C, while the reaction at room temperature led to an enantioselectivity of 69% ee (84%). In the presence of DBU, however, a satisfactory enantioselectivity was recorded (86% ee) in the reaction at room temperature.



Metal salt	Amine base	Solvent	Temp/°C	Time/h	Yield/%	ee %
$Ni(ClO_4)_2•6H_2O$	Et_3N	CH_2Cl_2	rt	24	96	60
$Ni(ClO_4)_2$	Et_3N	CH_2Cl_2	rt	55	84	69
$Ni(ClO_4)_2$	Et_3N	CH_2Cl_2	-40	180	83	0
$Ni(ClO_4)_2•6H_2O$	Proton sponge	CH_2Cl_2	-40	48	81	79
$Ni(ClO_4)_2•6H_2O$	*i*-Pr_2EtN	CH_2Cl_2	rt	24	67	76
$Ni(ClO_4)_2•6H_2O$	2,6-Lutidine	CH_2Cl_2	rt	24	76	63
$Ni(ClO_4)_2•6H_2O$	2,6-Lutidine	CH_2Cl_2	-40	48	74	75
$Ni(ClO_4)_2•6H_2O$	DBU	CH_2Cl_2	rt	36	63	86
$Ni(ClO_4)_2•6H_2O$	Et_3N	THF	rt	19	74	62
$Ni(ClO_4)_2•6H_2O$	Et_3N	THF	-40	96	96	86
$Ni(ClO_4)_2•6H_2O$	Proton sponge	THF	rt	30	90	57
$Ni(ClO_4)_2•6H_2O$	Proton sponge	THF	-40	67	67	10
$Ni(ClO_4)_2•6H_2O$	*i*-Pr_2EtN	THF	rt	5	75	50
$Ni(ClO_4)_2•6H_2O$	*i*-Pr_2EtN	THF	0	96	50	36
$Ni(ClO_4)_2•6H_2O$	*i*-Pr_2EtN	THF	-20	168	61	86
$Ni(ClO_4)_2•6H_2O$	2,6-Lutidine	THF	rt	5	75	66
$Ni(ClO_4)_2•6H_2O$	DBU	THF	rt	5	64	71
$Zn(ClO_4)_2•6H_2O$	Et_3N	THF	rt	115	48	88
$Zn(ClO_4)_2•6H_2O$	Proton sponge	THF	-40	133	82	85
$Zn(ClO_4)_2•6H_2O$	*i*-Pr_2EtN	THF	rt	120	35	89
$Zn(ClO_4)_2•6H_2O$	2,6-Lutidine	THF	rt	120	14	85
$Zn(ClO_4)_2•6H_2O$	DBU	THF	rt	120	14	85

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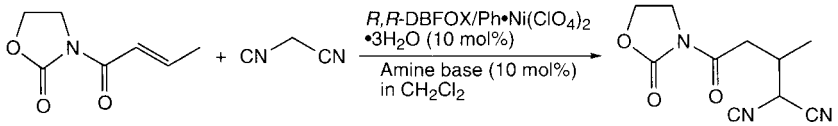
Scheme 7.48

The *R,R*-DBFOX/Ph·$Ni(ClO_4)_2·3H_2O$ complex-catalyzed Michael addition reactions in THF were, on the other hand, quite accelerated in the presence of amine bases. Effect of reaction temperatures on enantioselectivities also depended upon the nature of the Lewis bases used. Higher selectivities were observed at a lower temperature in the presence of triethylamine, but the opposite tendency was seen in the case of proton sponge. In the reactions using *N,N*-diisopropylethylamine, the highest selectivity (86% ee) appeared at –20 °C. Especially interesting was the high enantioselectivities observed in the zinc(II) aqua complex-catalyzed reactions in THF at room temperature, albeit the chemical yields were not satisfactory in all cases. It

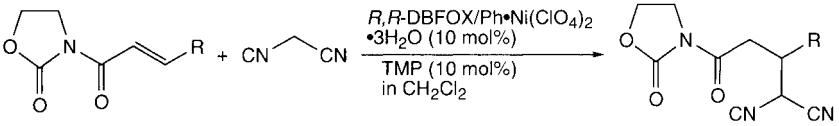
seemed likely that the zinc(II) complex catalyst was deactivated in the presence of amine bases in THF at room temperature. Thus, the catalytic activity was comparable, to that of the nickel(II) aqua complex-catalyzed reaction, at –40 °C in the reaction catalyzed by the zinc(II) aqua complex.

As shown above, it was not so easy to optimize the Michael addition reactions of 1-crotonoyl-3,5-dimethylpyrazole in the presence of the *R,R*-DBFOX/Ph·Ni$(ClO_4)_2 \cdot 3H_2O$ catalyst because a simple tendency of influence to enantioselectivity is lacking. Therefore, we changed the acceptor to 3-crotonoyl-2-oxazolidinone in the reactions of malononitrile in dichloromethane in the presence of the nickel(II) aqua complex (10 mol%) (Scheme 7.49). For the Michael additions using the oxazolidinone acceptor, dichloromethane was better solvent than THF and the enantioselectivities were rather independent upon the reaction temperatures and Lewis base catalysts. Chemical yields were also satisfactory.



Amine base	Temp/°C	Time/h	Yield/%	ee %
Et_3N	-40	72	80	80
Proton sponge	-20	18	92	85
Proton sponge	-30	48	90	84
i-Pr_2EtN	-20	24	quant	87
i-Pr_2EtN	-40	120	85	85
DBU	-20	96	70	87
N,N-Dibenzylamine	-20	32	quant	82
N,N-Dicyclohexylamine	-20	8	85	82
TMP	0	2	quant	81
TMP	-20	6	90	85
TMP	-40	96	98	81
TMP	-78	168	81	7

Scheme 7.49



R	Temp/°C	Time/h	Yield/%	ee %
Me	-20	6	90	85
n-Pr	rt	4	quant	82
n-Pr	-20	96	quant	86
i-Pr	-20	48	90	87
t-Bu	0	168	58	90
t-Bu	-20	168	38	94
Ph	rt	96	95	75

Scheme 7.50

Finally we have performed the Michael addition reactions of malononitrile and 3-(2-alkenoyl)-2-oxazolidinones in dichloromethane in the presence of the *R,R*-DBFOX/Ph·Ni(ClO_4)$_2$·3H_2O and TMP (10 mol% each). Enantioselectivities were a little lower than 90% ee for acceptors having a variety of *β*-substituents. The best selectivity was 94% ee in the reaction of *t*-butyl-substituted acceptor (Scheme 7.50).

7.6 Conclusion

In conclusion, the transition metal aqua complexes of *R,R*-DBFOX/Ph ligand have some remarkable features:

(i) the rare tridentate, *trans*-chelating, and neutral chiral ligand;
(ii) complexation with transition metal perchlorates give isolable aqua complexes;
(iii) the aqua complexes can be stored in an open air without loss of activity;
(iv) the aqua complexes have high tolerance against coordinating or nucleophilic reagents;
(v) high induction of enantioselectivity;
(vi) the rigid and stable structure of metal complexes makes easy to figure out the transition state structure;
(vii) successful applications to 1,3-dipolar cycloadditions;
(viii) successful applications to conjugate additions using coordinating reagents; and
(ix) the possibility of a chiral Lewis acid catalyst having an ability of molecular recognition.

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8
Theoretical Calculations of Metal-catalyzed Cycloaddition Reactions

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8.1
Introduction

Metal-catalyzed cycloaddition reactions have been in intensive development in recent years and many aspects of the various types of reaction are covered in the many different books, reviews, and numerous research papers dealing with the topic. The focus of the work performed in the field of metal-catalyzed cycloaddition reactions has been devoted to the development of the reactions; i.e. screening reaction conditions (e.g. different metals and ligands), substrates, and showing that the reaction developed might have a potential for the synthesis of products of general interests.

Compared with very intensive work in the development of metal-catalyzed cycloaddition reactions, the work in the field of understanding these reaction from a theoretical point of view is very limited. Although there are many reasons for this, the main reason is probably that only recently has it become possible to perform trustworthy calculations for metal systems to obtain reliable information about reaction courses for metal-catalyzed cycloaddition reactions.

This chapter will try to cover some developments in the theoretical understanding of metal-catalyzed cycloaddition reactions. The reactions to be discussed below are related to the other chapters in this book in an attempt to obtain a coherent picture of the metal-catalyzed reactions discussed. The intention with this chapter *is not* to go into details of the theoretical methods used for the calculations – the reader must go to the original literature to obtain this information. The examples chosen are related to the different chapters, i.e. this chapter will cover carbo-Diels-Alder, hetero-Diels-Alder and 1,3-dipolar cycloaddition reactions. Each section will start with a description of the reactions considered, based on the frontier molecular orbital approach, in an attempt for the reader to understand the basis molecular orbital concepts for the reaction.

8.2
Carbo-Diels-Alder Reactions

8.2.1
Frontier-molecular-orbital Interactions for Carbo-Diels-Alder Reactions

One cannot discuss Lewis acid-catalyzed cycloaddition reactions in the present context without trying to understand the reaction course mechanistically, e.g. using a frontier molecular orbital (FMO) point of reasoning, or theoretical calculations of transition state structures.

Most carbo-Diels-Alder reactions discussed can be classified into two types of $[_{\pi}2_s + _{\pi}4_s]$ cycloadditions, normal and inverse electron-demand reactions, based on the relative energies of the FMOs of the diene and the dienophile. The two general cases are the interaction of a dienophile, having a low LUMO energy, with the HOMO of the diene (Fig. 8.1, left), and the interaction of a dienophile, having a high HOMO energy, with the LUMO of a diene (Fig. 8.1, right) [1].

The reactivity of the carbo-Diels-Alder reaction, as well as the other reactions considered in this chapter, can be accounted for by a simple FMO line of reasoning, i.e., the energy term from second-order perturbation theory:

$$\Delta E \propto \frac{c_{HOMO} \times c_{LUMO}}{E_{HOMO} - E_{LUMO}} \quad (1)$$

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where c_{HOMO} and c_{LUMO} are the orbital coefficients at the reacting atoms in the HOMO and LUMO, respectively. $E_{HOMO} - E_{LUMO}$ in the denominator is the en-

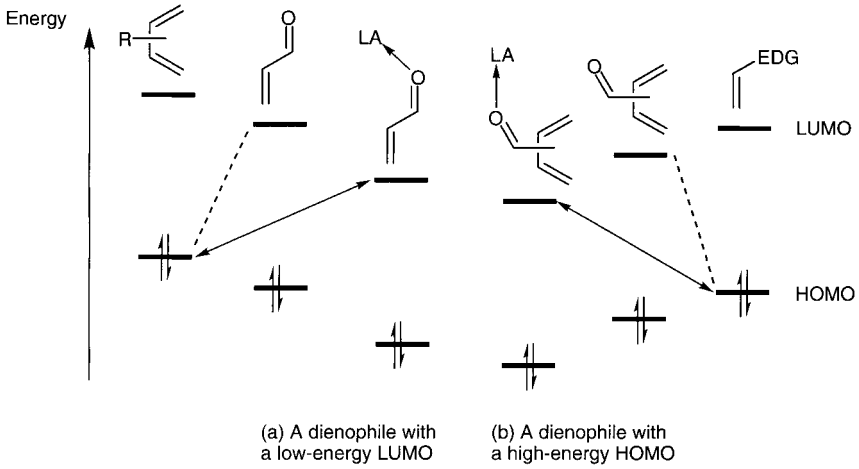


Fig. 8.1 Frontier-orbital interaction for carbo-Diels-Alder reactions. (a) The interaction of a dienophile with a low-energy LUMO, in the absence and presence of a Lewis acid (LA), with a diene. (b) The interaction of a dienophile with a high-energy HOMO with a diene, in the absence, and presence of a Lewis acid

ergy difference between the HOMO and LUMO. In Eq. (1), a very simplified expression of second-order perturbation theory, it is assumed that it is mainly the HOMO-LUMO interaction which determines the reactivity.

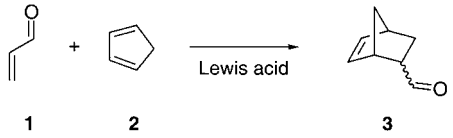
The coordination of a Lewis acid to the alkene e.g. via a conjugated carbonyl group (Fig. 8.1, left) will lower the energy of the FMOs of the alkene, relative to the uncoordinated alkene. The lowering in energy of the $LUMO_{alkene}$ will lead to a decrease in energy difference between E_{HOMO} of the diene and E_{LUMO} of the alkene coordinated to the Lewis acid, compared to the interaction in the absence of the Lewis acid. The decrease in E_{LUMO} of the alkene coordinated to the Lewis acid leads to an increase in ΔE in Eq. (1) and thus a faster reaction should be expected. In a similar manner will coordination of a Lewis acid to the diene lower the energy of the FMOs, relative to unperturbed diene (Fig. 8.1, right) and a similar argument as above will also lead to an increased reactivity in this case, compared to the Diels-Alder reaction in the absence of a catalyst. In this simplified version, the increase in reactivity of the alkene with the diene in the presence of Lewis acid catalysts is due to a change of the FMO-energy of the substrate interacting with the catalyst. However, it should also be mentioned that other factors such as the coordination ability of the substrate to the Lewis acid can alter the reactivity significantly.

Most Lewis acid-catalyzed carbo-Diels-Alder reactions belong to the interactions outlined to the left in Fig. 8.1 and in the following only theoretical calculations of this type will be considered.

8.2.2
Activation of the Dienophile by Lewis Acids, Interactions, Reaction Course, and Transition-state Structures

Houk et al. were probably among the first to investigate the Lewis acid activation of a substrate in relation to cycloaddition reactions [2]. In an attempt to understand the increase in reaction rate, regio- and stereoselectivity in an *exo-endo* sense for Lewis acid-catalyzed carbo-Diels-Alder reactions of an α,β-unsaturated carbonyl compound such as acrolein **1** with cyclopentadiene **2** (Scheme 8.1) theoretical investigations were performed. It was shown that these phenomena were simply rationalized applying FMO theory using CNDO/2 calculations. Acrolein **1** was used for these investigations and coordination of the non-bonding electrons of the carbonyl oxygen atom of the α,β-unsaturated carbonyl compound led to a lowering of the energies of the π-orbitals, as well as a redistribution of the FMOs of protonated acrolein – a simple model for a Lewis acid-coordinated dienophile (Fig. 8.2).

The FMOs of acrolein to the left in Fig. 8.2 are basically slightly perturbed butadiene orbitals, while the FMOs of protonated acrolein resemble those of an allyl cation mixed in with a lone-pair orbital on the oxygen atom (Fig. 8.2, right). Based on the FMOs of protonated acrolein, Houk et al. [2] argued that the predominant interaction in a "normal electron-demand" carbo-Diels-Alder reaction is between the dienophile LUMO and diene HOMO (Fig. 8.1, left). This interaction is greatly



Scheme 8.1

facilitated by Lewis acid complexation, which lowers the dienophile LUMO energy to a large extent, leading to a better LUMO-HOMO interaction as shown for the interaction to the right in Fig. 8.2.

The coordination of the dienophile to a Lewis acid (in the calculations a proton was used as the Lewis acid) leads also to an increase in regioselectivity. The regioselectivity of reactions of electron-rich, or conjugated dienes, with electron-deficient dienophiles is also controlled by the diene HOMO-dienophile LUMO interaction. From Fig. 8.2 it appears that the difference in magnitudes of the LUMO coefficients at carbon atoms 1 and 2 of acrolein (C_1^2–C_2^2=0.20) is smaller than the same difference for protonated acrolein (C_1^2–C_2^2=0.30–0.43) so that the reaction of the latter should be considerable more regioselective than the former in accordance with the experimental results [3].

The *endo*/*exo* ratio also increases in the presence of Lewis acid catalysis, e.g. reacts cyclopentadiene with methyl acrylate to give an *endo*/*exo* ratio of 82:18 and 99:1, for the uncatalyzed and the $AlCl_3$-catalyzed reactions, respectively [4]. This increase in stereoselectivity can also be accounted for by a FMO way of reasoning as shown in Fig. 8.3. The $diene_{HOMO}$-$dienophile_{LUMO}$ second-order interaction between the carbonyl carbon atom and C-2 of the diene is greatly increased in the Lewis acid-catalyzed reaction, because the atomic orbital coefficient of the coordinated carbonyl carbon atom becomes very large by coordination to the Lewis acid (Fig. 8.3 b). The increase in second-order orbital interaction might lead to a "tigh-

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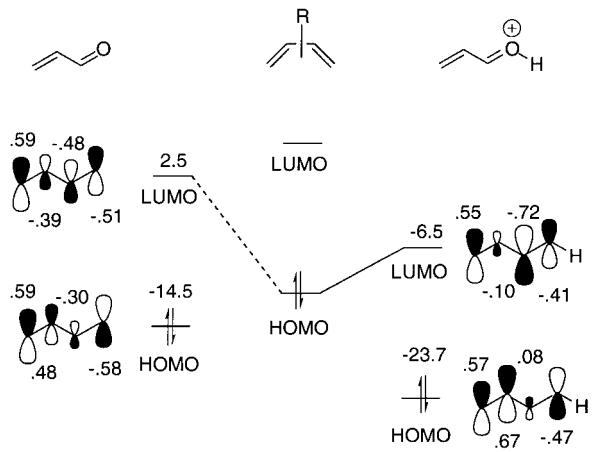

Fig. 8.2 Frontier-orbital coefficients and energies (eV) for acrolein and protonated acrolein [2]

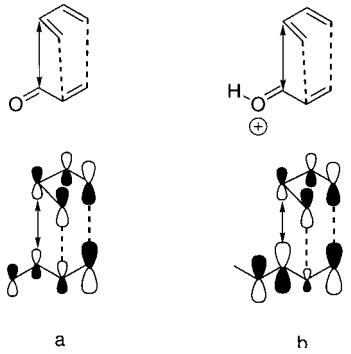

Fig. 8.3 Diene HOMO-dienophile LUMO interaction of *endo* transition state for the reaction of cyclopentadiene with acrolein (a) and protonated acrolein (b) [2]

ter" transition state in the Lewis acid-catalyzed reaction which can have an effect for the enantioselectivity in the chiral Lewis acid-catalyzed reactions [2].

Houk et al. concluded that this FMO model imply increased asynchronicity in the bond-making processes, and if first-order effects (electrostatic interactions) were also considered, a two-step mechanisms, with cationic intermediates become possible in some cases. It was stated that *the model proposed here shows that the phenomena generally observed on catalysis can be explained by the concerted mechanism, and allows predictions of the effect of Lewis acid on the rates, regioselectivity, and stereoselectivity of all concerted cycloadditions, including those of ketenes, 1,3-dipoles, and Diels-Alder reactions with "inverse electron-demand"* [2].

The carbo-Diels-Alder reaction of acrolein with butadiene (Scheme 8.1) has been "the standard reaction" studied by theoretical calculations in order to investigate the influence of Lewis acids on the reaction course and several papers deal with this reaction. As an extension of an ab-initio study of the carbo-Diels-Alder reaction of butadiene with acrolein [5], Houk et al. investigated the transition-state structures and the origins of selectivity of Lewis acid-catalyzed carbo-Diels-Alder reactions [6]. Four different transition-state structures were considered (Fig. 8.4). Acrolein can add either *endo* (N) or *exo* (X), in either *s-cis* (C) or *s-trans* (T), and the Lewis acid coordinates to the carbonyl in the molecular plane, either *syn* or *anti* to the alkene.

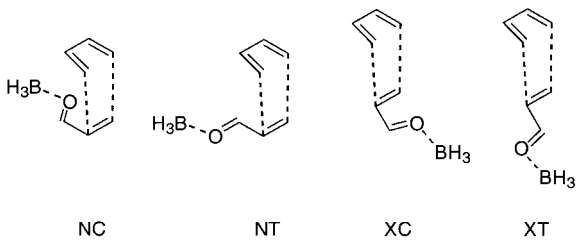

Fig. 8.4 The four different transition-state structures considered for the Diels-Alder reaction of acrolein with a diene in the presence of a Lewis acid (BH_3). The diene can add either *endo* (N) or *exo* (X) with acrolein being *s-cis* (C) or *s-trans* (T) and the Lewis acid coordinates to the carbonyl in the molecular plane, either *syn* or *anti* to the alkene

Both experimental [7] and theoretical [8] investigations have shown that the *anti* complexes of acrolein and boranes are the most stable and the transition states were located only for these four *anti* complexes. The most stable transition-state structure was calculated (RHF/3-21G) to be NC, while XT is the least stable of the four located. The activation energy has been calculated to be 21.6 kcal mol^{-1} for the catalyzed reaction, which is substantially above the experimental value of 10.4 ± 1.9 kcal mol^{-1} for the $AlCl_3$-catalyzed addition of methyl acrylate to butadiene [4a]. The transition-state structure NC is shown in Fig. 8.5.

The mechanism of the carbo-Diels-Alder reaction has been a subject of controversy with respect to synchronicity or asynchronicity. With acrolein as the dienophile complexed to a Lewis acid, one would not expect a synchronous reaction. The C1–C6 and C4–C5 bond lengths in the NC-transition-state structure for the BF_3-catalyzed reaction of acrolein with butadiene are calculated to be 2.96 Å and 1.932 Å, respectively [6]. The asynchronicity of the BF_3-catalyzed carbo-Diels-Alder reaction is also apparent from the pyramidalization of the reacting centers; C4 and C5 of NC (the short C–C bond) is pyramidalized by 11°, while C1 and C6 (the long C–C bond) are nearly planar. The lowest energy transition-state structure (NC) has the most pronounced asynchronicity, while the highest energy transition-state structure (XT) is more synchronous.

The asynchronicity in the NC-transition state can be accounted for by the FMOs (Figs 8.2 and 8.3). The large LUMO coefficient of the β-carbon atom of acrolein makes this atom more electrophilic than the carbon atom to the carbonyl, which has a very small coefficient. The major interaction for this carbo-Diels-Alder reaction is the $LUMO_{acrolein}$-$HOMO_{diene}$ and the greater overlap of the β-carbon atom with the diene HOMO gives a stronger and shorter bond in the transition state. Although, the NC-transition state is asynchronous, the calculations indicated that the reaction is still concerted, since no energy minimum corresponding to an intermediate was found [6]. There is also a significant difference in change separation in the transition-state structure for the uncatalyzed reaction, compared to the BF_3-catalyzed Diels-Alder reaction. In the uncatalyzed reaction corresponding to the NC-transition state, only 0.09 electron has been transferred from butadiene to acrolein, while in the catalyzed transition-state structure NC there is a net transfer of 0.31 electrons [6].

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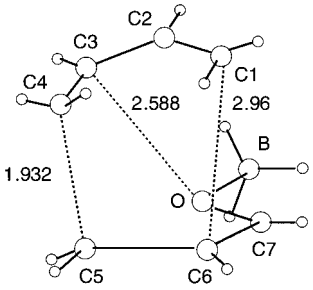

Fig. 8.5 The calculated transition-state structure for the reaction of acrolein with butadiene leading to carbo-Diels-Alder adduct catalyzed by BH_3 using a RHF/3-21G basis set [6]

An important contribution for the *endo* selectivity in the carbo-Diels-Alder reaction is the second-order orbital interaction [1]. However, no bonds are formed in the product for this interaction. For the BF_3-catalyzed reaction of acrolein with butadiene the overlap population between C1 and C6 is only 0.018 in the NC-transition state [6], which is substantially smaller than the interaction between C3 and O (0.031). It is also notable that the C3–O bond distance, 2.588 Å, is significant shorter than the C1–C6 bond length (2.96 Å), of which the latter is the one formed experimentally. The NC-transition-state structure can also lead to formation of vinyldihydropyran, i.e. a hetero-Diels-Alder reaction has proceeded. The potential energy surface at the NC-transition-state structure is extremely flat and structure NCA (Fig. 8.6) lies on the surface-separating reactants from product [6]. The transition-state structure NCA has a shorter C1–C6 bond distance (2.728 Å) and a longer C3–O bond distance (2.820 Å) than NC. The calculated transition-state energy of NCA is only 0.05 kcal mol^{-1} higher in energy than NC at a 3-21G level, whereas RHF/6-31G* single-point calculations place NCA 0.2 kcal mol^{-1} below NC. Except for the slight twisting of butadiene relative to the BF_3-activated acrolein, which leads to the different in bond lengths, there are no further major differences between NC and NCA [6].

The two transition states in Figs 8.5 and 8.6 correspond in principle to a metal-catalyzed carbo-Diels-Alder reaction under normal electron-demand reaction conditions and a hetero-Diels-Alder reaction with inverse electron-demand of an enone with an alkene. The calculations by Houk et al. [6] indicated that with the basis set used there were no significant difference in the reaction course.

In an investigation by Yamabe et al. [9] of the fine tuning of the [4+2] and [2+4] cycloaddition reaction of acrolein with butadiene catalyzed by BF_3 and $AlCl_3$ using a larger basis set and more sophisticated calculations, the different reaction paths were also studied. The activation energy for the uncatalyzed reaction were calculated to be 17.52 and 16.80 kcal mol^{-1} for the *exo* and *endo* transition states, respectively, and is close to the experimental values for *s-trans*-acrolein. For the BF_3-catalyzed reaction the transition-state energies were calculated to be 10.87 and 6.09 kcal mol^{-1}, for the *exo*- and *endo*-reaction paths, respectively [9]. The calculated transition-state structures for this reaction are very asynchronous and similar to those obtained by Houk et al. The *endo*-reaction path for the BF_3-catalyzed reaction indicates that an inverse electron-demand C3–O bond formation (2.635 Å

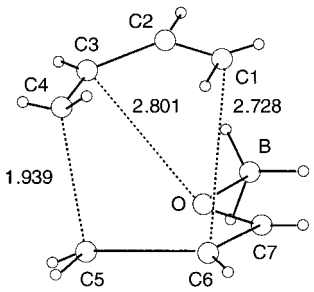

Fig. 8.6 The calculated transition-state structure for the reaction of acrolein with butadiene leading to formation of vinyldihydropyran by a hetero-Diels-Alder adduct catalyzed by BH_3 using a RHF/3-21G basis set [6]

in the transition state) takes place instead of the C1–C6 bond formation (3.119 Å in the transition state). Furthermore, intrinsic reaction coordinates (IRS) show that the end of the reaction path was a [2+4] hetero-Diels-Alder adduct and not the (expected) carbo-Diels-Alder [4+2] product. It was suggested that the vinyldihydropyran obtained from the hetero-Diels-Alder reaction could isomerize to the final [4+2] product with a transition state energy of 28.07 kcal mol^{-1}. This reaction of acrolein with butadiene was also investigated for $AlCl_3$ as the Lewis acid [9]. The transition-state energies for the *exo*- and *endo*-reaction paths were calculated to be 6.15 and 2.64 kcal mol^{-1}. The IRC calculations showed that the product of the reaction was dependent of the method of calculations; the RHF/3-21G transition state gave a [4+2] adduct, while the RHF/6-31G* and 3-21G gave the [2+4] adduct. These calculations demonstrate that the potential energy surface around the $AlCl_3$-containing transition state is very flat and that the selectivity depends on the Lewis acid, as well as the computational methods.

The question of the BF_3-catalyzed [4+2] or [2+4] cycloaddition reaction path of acrolein with butadiene was further addressed by Garcia, Mayoral et al. [10a]. They first used a MP2/6-31G* basis set search starting out from the RHF/6-31G* transition state and found notable differences to the transition state obtained by RHF. The C1–C6 (see Fig. 8.5 for numbering) is now only 2.805 Å, and it becomes shorter than the C3–O distance which passes from 2.807 to 2.827 Å. Also, the C4–C5 distance increases from 1.936 to 2.209 Å. The IRC shows the concertedness and asynchronicity of the reaction, the C5–C6 bond is formed first, and, when this bond is almost formed, the C1–C6 bond progress rapidly towards the adduct final value of 1.532 Å. The C3–O distance decreases slowly at the first stage of the reaction path and then increases until its final value of 3.636 Å, due to the conformational change of the cyclohexene ring and the rotation of the formyl ring in the product. The calculations at the MP2 level showed thus that the [4+2] cycloaddition was preferred and it was concluded that the BF_3-catalyzed Diels-Alder reaction of butadiene and acrolein follows a concerted and asynchronous reaction mechanism, even for the *endo-s-cis* transition state, although the inclusion of electronic correlation corrections is essential to achieve this result.

Further studies by Garcia, Mayoral et al. [10b] also included DFT calculations for the BF_3-catalyzed reaction of acrolein with butadiene and it was found that the B3LYP transition state also gave the [4+2] cycloadduct, as happens for the MP2 calculations. The calculated activation energy for lowest transition-state energy was between 7.3 and 11.2 kcal mol^{-1} depending on the basis set used. These values compare well with the activation enthalpies experimentally determined for the reaction of butadiene with methyl acrylate catalyzed by $AlCl_3$ [4a, 10].

The *endo exo* selectivity for the Lewis acid-catalyzed carbo-Diels-Alder reaction of butadiene and acrolein deserves a special attention. The relative stability of *endo* over *exo* in the transition state accounts for the selectivity in the Diels-Alder cycloadduct. The Lewis acid induces a strong polarization of the dienophile FMOs and change their energies (see Fig. 8.2) giving rise to better interactions with the diene, and for this reason, the role of the possible secondary-orbital interaction must be considered. Another possibility is the [4+3] interaction suggested by Singleton

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[11], which is a bonding interaction between C1 and C7 (see numbering in Fig. 8.5) which has been explained on the basis of FMO considerations. However, it was pointed out by Garcia, Mayoral et al. [10b] that the *endo* rule seems to keep its validity in this particular system, because the secondary-orbital interaction are globally more important in the *endo*-transition state, because of their number and/or strength.

An interesting comparison of the role of the BCl_3, $AlCl_3$, $GaCl_3$, $InCl_3$, $ZnCl_2$, $SnCl_2$ and $SnCl_4$ as the Lewis acid for the carbo-Diels-Alder reaction of butadiene with acrolein, and the role of solvent for the reaction, has been performed by Yamabe et al. [12]. For all the Lewis acid studied, first a precursor – a reactant-like complex – was identified, followed by location of the transition state, and finally the carbo-Diels-Alder cycloadduct was found. In the presence of the Me_2O as the solvent a more loose transition state was calculated and the coordination of the solvent to the Lewis acid weakens its catalytic strength. For the Lewis acids considered it was found that the coordination of BCl_3 to acrolein is so strong that the Me_2O molecule was practically unbound to the boron atom of BCl_3. The strongest Lewis acids were BCl_3 and $SnCl_4$ and it was pointed out that the transition-state structures for these Lewis acids was a three-center interaction as shown to the left in Fig. 8.7, while the more weak Lewis acids give a two-center interaction in the transition-state structure as shown to the right in Fig. 8.7.

The influence of alkyl substituents on the asynchronous transition-state structure of the BF_3-catalyzed carbo-Diels-Alder reaction of α,β-unsaturated aldehydes with 1,1-dimethyl-1,3-butadiene derivatives has been investigated by Dai et al. [13]. In a combined experimental and theoretical investigation it was found that the β-alkyl group in the dienophile gave a steric interaction in the transition-state structure which supported the asynchronous transition-state structure for the Lewis acid-catalyzed carbo- and hetero-Diels-Alder reactions. The calculated transition-state energies were of similar magnitude as obtained in other studies of these BF_3-catalyzed carbo-Diels-Alder reactions.

A frequently used catalytic system used for the catalytic enantioselective carbo-Diels-Alder reaction of *N*-alkenoyl-1,3-oxazolidin-2-one **4** is the chiral TADDOL–Ti(IV) **6** [14] complexes (Scheme 8.2; see Chapter 1 in this book, by Hayashi) [15].

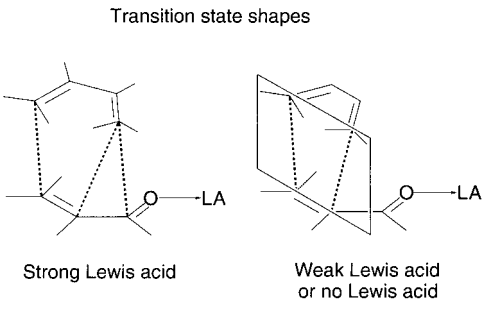
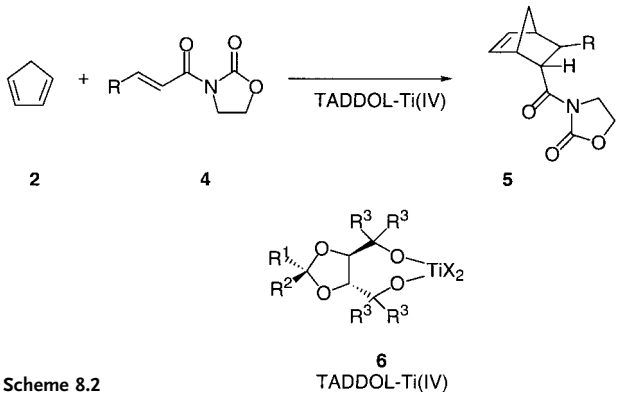


Fig. 8.7 The different transition-state shapes for the carbo-Diels-Alder reaction in the pressence of a strong Lewis acid (left) – a three center interaction – and a weak Lewis acid (right) [12]



Scheme 8.2

The mechanism for the catalytic enantioselective carbo-Diels-Alder reaction of *N*-alkenoyl-1,3-oxazolidin-2-one **4** with, e.g., cyclopentadiene **2** catalyzed by chiral TADDOL–Ti(IV) complexes **6** has been the subject for several investigations and especially, the structure of the intermediate for the reaction has been subject to controversy. The coordination of **4** to **6** can give five diastereomeric complexes **A**, $\mathbf{B_1}$, $\mathbf{B_2}$, $\mathbf{C_1}$, and $\mathbf{C_2}$, as outlined in Fig. 8.8.

An X-ray structure of the complex formed between 3-cinnamoyl-1,3-oxazolidin-2-one and a chiral TADDOL-Ti(IV) complex (see Chapters 1 and 6 by Hayashi and Gothelf, respectively) has been characterized [16]. The structure of this complex has the chiral TADDOLate and cinnamoyloxazolidinone ligands coordinated to titanium in the equatorial plane and the two chloride ligands in the axial plane and is similar to **A** in Fig. 8.8. The chiral discrimination was proposed to be due to

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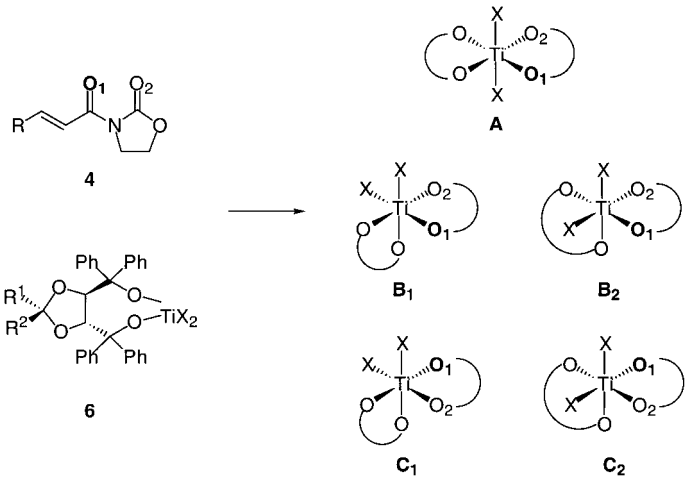
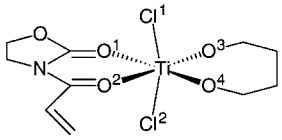


Fig. 8.8 The possible coordination modes of *N*-alkenoyl-1,3-oxazlidin-2-one **4** to chiral TADDOL-Ti(IV) complexes **6** leading to the five diastereomeric complexes **A**, $\mathbf{B_1}$, $\mathbf{B_2}$, $\mathbf{C_1}$, and $\mathbf{C_2}$

the pseudo-axial phenyl group of the chiral ligand which seems to shield one of faces of the cinnamoyloxazolidinone and this model has been proposed to account for the enantioselection of the both the carbo-Diels-Alder and 1,3-dipolar cycloaddition reactions catalyzed by these complexes [17]. However, Seebach et al. [18] and DiMare et al. [19] have suggested that, although complex **A** is the major intermediate in solution, the minor intermediates, $\mathbf{B_1}$ and $\mathbf{B_2}$, in which the enoate moiety is in the *trans* position with the chloride ligands, have a higher degree of Lewis acid-activation, and hence to be the most reactive intermediate.

In an attempt to obtain insight into the intermediate for these TADDOL-Ti(IV)-catalyzed carbo-Diels-Alder reactions Mayoral et al. [20] have performed a series of ab-initio calculations of the model complexes **A–C** shown in Fig. 8.8. They used model complexes formed between 3-acroloyl-1,3-oxazolidin-2-one and an achiral analog of TADDOL-$TiCl_2$, namely that derived from 1,4-butanediol **MA-MC** (Fig. 8.9). The geometries of **MA-MC** were optimized and some data are shown in Fig. 8.9. For **MA** the data obtained for X-ray structure of **A** shown in the brackets and it appears that the calculated results are in good agreement with the experimental results. The most stable complex was calculated to be **MA** in accordance with the experimental results [16–19]. Complex **MC** is the next most stable complex, but with a difference of more than 5 kcal mol^{-1} with respect to **MA**. Finally, **MB** is the most unstable complex, although it is close in energy (1–2 kcal mol^{-1}) to **MC**. In order to account for the reactivity of **MA-MC** the LUMO energy of each complex has been calculated. The LUMO, which essentially corresponds to the π^* MO of the α,β-unsaturated carbonyl moiety of the dienophile exhibits a strong polarization towards the carbonyl carbon atom as expected from the coordination to the Lewis acid. The lowest LUMO energy is that of **MB** followed by **MC** and **MA**, the LUMO energy difference between **MB** and **MA** is ca. 4 kcal mol^{-1} (< 0.2 eV) and is basis-set dependent. The charge transfer from the dienophile to the titanium complex gave for **MA** 0.144 electrons, while 0.162 and 0.148 were obtained for **MB** and **MC**, respectively. Mayoral et al. [20] concluded on the basis of the theoretical calculations, that **MB** experiences the highest degree of Lewis acid-activation by the TADDOL-$TiCl_2$ complex, which is in line with the LUMO energy values and that intermediate **MB**, which exists in small concentrations under the reaction conditions is responsible for the reaction course of these carbo-Diels-Alder reaction. However, at the present it has not been clearly confirmed whether or not the *trans* and/or *cis* complex(es) are real reactive intermediates.

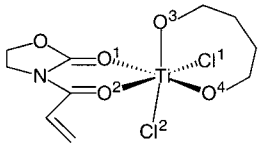
Several papers have been using theoretical calculations at various levels of sophistication for different types of Diels-Alder reactions and often in relation to experimental investigations. Branchadell et al. [21] have investigated the effect of $AlCl_3$ on the reaction of (*Z*)-(*S*)-4,5-(2,2-propylidenedioxy)pent-2-enoate and (*Z*)-(*S*)-4,5-(2,2-propylidenedioxy)pent-2-enoate acid with cyclopentadiene (Scheme 8.3) at the B-LYP/6-31G* level of calculations. The transition state for the latter reactions has been calculated to have the lowest energy barrier of 14.6 kcal mol^{-1} in qualitative agreement with the experimental results. The effect of $AlCl_3$ on the *endo-exo* selectivity can be attributed to both steric and electronic effects. The latter relates to the complexation of the enoate molecule to the catalyst favoring an *s-trans* con-



MA

Ti-Cl^1: 2.424 Å (2.356 Å)
Ti-Cl^2: 2.398 Å (2.356 Å)
Ti-O^1: 2.192 Å (2.157 Å)
Ti-O^2: 2.258 Å (2.135 Å)
Ti-O^3: 1.727 Å (1.784 Å)
Ti-O^4: 1.733 Å (1.762 Å)

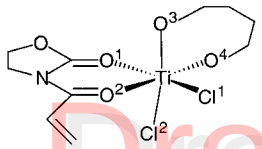
Cl^1TiCl^2: 157.4° (164.4°)
O^1TiO^2: 74.2° (79.0°)
O^3TiO^4: 97.0° (97.5°)



MB

Ti-Cl^1: 2.306 Å
Ti-Cl^2: 2.523 Å
Ti-O^1: 2.271 Å
Ti-O^2: 2.129 Å
Ti-O^3: 1.752 Å
Ti-O^4: 1.731 Å

Cl^1TiCl^2: 93.9°
O^1TiO^2: 73.7°
O^3TiO^4: 95.3°



MC

Ti-Cl^1: 2.318 Å
Ti-Cl^2: 2.530 Å
Ti-O^1: 2.265 Å
Ti-O^2: 2.167 Å
Ti-O^3: 1.749 Å
Ti-O^4: 1.726 Å

Cl^1TiCl^2: 93.2°
O^1TiO^2: 73.5°
O^3TiO^4: 95.3°

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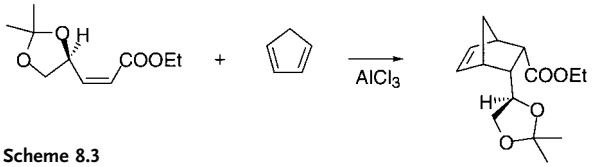
Fig. 8.9 The calculated model complexes formed between 3-acroloyl-1,3-oxazolidin-2-one and an achiral analog of TADDOL-$TiCl_2$, namely that derived from 1,4-butanediol **MA–MC** [20]. The number in the brackets refer to data obtained for X-ray structure [16]

formation of the ester moiety which leads to an increase of the stabilizing interactions favoring the *endo* transition state. The *syn-anti* selectivity has been found to be due to steric effects. The transition-state structures for this reaction also show the asynchronous reaction course.



Scheme 8.3

The reaction of methyl vinyl ketone with furan catalyzed by BF_3 was studied by Babiano et al. [22]. The transition states predicted were also relatively concerted and highly asynchronous for all the reaction paths studied.

Yamamoto et al. have developed a catalytic enantioselective carbo-Diels-Alder reaction of acetylenic aldehydes **7** with dienes catalyzed by chiral boron complexes (Fig. 8.10) [23]. This carbo-Diels-Alder reaction proceeds with up to 95% ee and high yield of **8** using the BLA catalyst. The reaction was also investigated from a theoretical point of view using ab-initio calculations at a RHF/6-31G* basis set. The four different transition states in Fig. 8.10 were considered with BF_3 as a model for the BLA catalyst in the theoretical calculations. It was found that the lowest transition-state energy for the BF_3-catalyzed reactions was calculated to be 21.3 kcal mol^{-1} for *anti-exo* transition state, while only 1.5 kcal mol^{-1} higher in energy the *syn-exo* transition state, was found. The uncatalyzed reaction was calculation to proceed via an *exo* transition state having an energy of 37.0 kcal mol^{-1}. The calculations indicated that the reaction proceeds predominantly by an *exo* transition-state structure and that it is enhanced by the coordination of the Lewis acid. The transition-state structures were also found to be more asynchronous in the presence of BF_3 Lewis acid compared with the uncatalyzed reactions.

A series of investigation using, e.g., semi-empirical calculations have also been performed [24]. These calculations are often used in relation with experimental investigations, as well as, e.g., the carbo-Diels-Alder reaction of acrolein with dienes.

We are now able to understand the Lewis acid-catalyzed normal electron-demand carbo-Diels-Alder reaction from a theoretical point of view. The calculated influence of the Lewis acids on the reaction rate, regio- and stereoselectivity in an

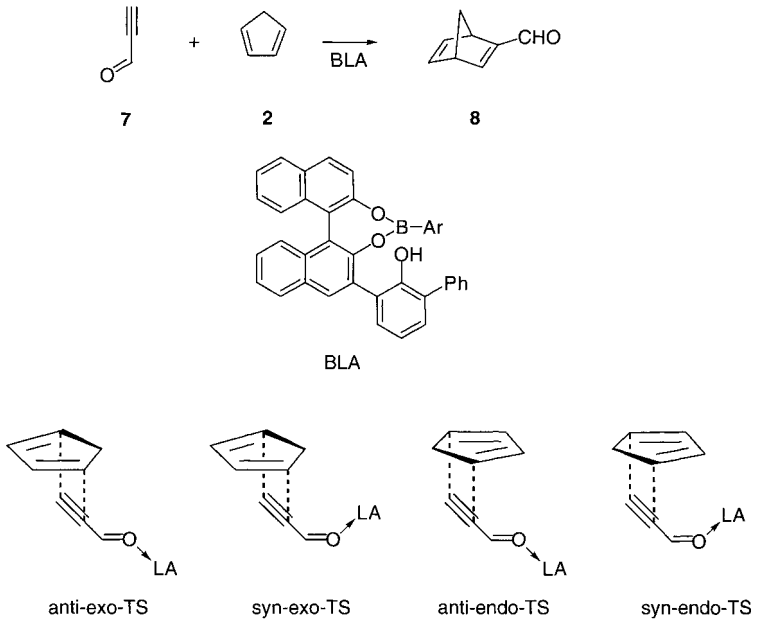


Fig. 8.10 The catalytic enantioselective carbo-Diels-Alder reaction of acetylenic aldehydes **7** with cyclopentadiene **2** catalyzed by chiral boron complexes (BLA) and the transition-state structures investigated by ab-initio calculations [23]

exo–endo sense α,β-unsaturated carbonyl compound with cyclopentadiene fits nicely the experimental results. The calculations indicate that the carbo-Diels-Alder reactions are still "concerted-like" – however, the presence of the Lewis acid makes the transition-state structures more asynchronous compared to the uncatalyzed reactions.

8.3 Hetero-Diels-Alder Reactions

8.3.1 Frontier-molecular-orbital Interactions for Hetero-Diels-Alder Reactions

Hetero Diels-Alder reactions can also be classified into two types of $[_\pi 2_s + _\pi 4_s]$ cycloadditions, the normal and inverse electron-demand hetero-Diels-Alder reactions, based on the relative energies of the FMOs of the diene and the dienophile (Fig. 8.11) [1 b].

The normal electron-demand reaction is a $HOMO_{diene}$-$LUMO_{dienophile}$-controlled hetero-Diels-Alder reaction which predominantly occurs between electron-rich dienes and electron-deficient dienophiles (Fig. 8.11, left – dotted line). The inverse electron-demand hetero-Diels-Alder reaction is primarily controlled by a $LUMO_{diene}$-$HOMO_{dienophile}$ interaction which can be found for e.g. enones and heteroanalogs reacting with alkenes having electron-donating groups (Fig. 8.11, right – dotted line).

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The basic concept of activation in hetero-Diels-Alder reactions is to utilize the lone-pair electrons of the carbonyl and imine functionality for coordination to the Lewis acid. The coordination of the dienophile to the Lewis acid changes the FMOs of the dienophile and for the normal electron-demand reactions a decrease of the LUMO and HOMO energies is observed leading to a better interaction with

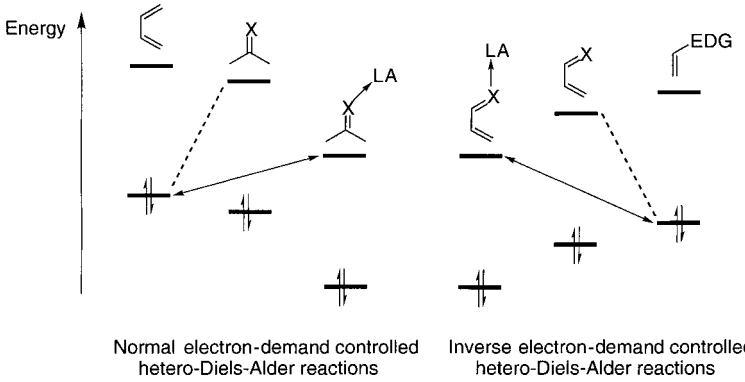

Fig. 8.11 An FMO diagram of the normal and inverse electron-demand hetero-Diels-Alder reactions, in the absence and presence of a Lewis acid

the dienophile (Fig. 8.11, left – full line). The energy difference between the $HOMO_{diene}$ and the $LUMO_{dienophile}$ is thus reduced compared with the absence of a Lewis acid which can account for the activating effect of the Lewis acid. The catalytic properties of the Lewis acid for the inverse electron-demand hetero-Diels-Alder reaction is due to the coordination of the Lewis acid to a heteroatom of the 1,3-diene leading to a decrease of the $LUMO_{diene}$ and $HOMO_{dienophile}$ energies, and thus, based on a FMO way of reasoning, a more favorable interaction with the electron-rich alkene takes place (Fig. 8.11, right – full line). Furthermore, the coordination to the Lewis acid alters also, to some extent, the distribution of the atomic orbital coefficients of the dienophile and the 1,3-diene. For a carbonyl compound an increase in the magnitude of the LUMO atomic orbital coefficient at the carbonyl carbon atom is observed making it more susceptible to the diene. However, this polarization may also influence on the reaction mechanism. It has been pointed out that the hetero-Diels-Alder reaction can change from a concerted non-synchronous mechanism to a stepwise mechanism depending on the substituents on the reacting species and reaction conditions.

Very few theoretical studies of hetero-Diels-Alder reactions have been performed [25] and, furthermore, theoretical studies of the Lewis acid-catalyzed hetero-Diels-Alder reactions are even more limited.

8.3.2
Normal Electron-demand Hetero-Diels-Alder Reactions

The transition-state structure of the hetero-Diels-Alder reaction is generally found to be unsymmetrical. Houk et al. have for the reaction of formaldehyde with 1,3-butadiene calculated the C–C and C–O bond lengths to be 2.133 Å and 1.998 Å, respectively, in the transition state using ab-initio calculations shown in Fig. 8.12 [25 b]. The reaction of formaldimine follows the same trend for the transition-state structure.

The hetero-Diels-Alder reaction of formaldehyde with 1,3-butadiene has been investigated with the formaldehyde oxygen atom coordinated to BH_3 as a model for a Lewis acid [25 b]. Two transition states were located, one with BH_3 *exo*, and one *endo*, relative to the diene. The former has the lowest energy and the calculated transition-state structure is much less symmetrical than for the uncatalyzed reaction shown in Fig. 8.12. The C–C bond length is calculated to be 0.42 Å longer, while the C–O bond length is 0.23 Å shorter, compared to the uncatalyzed reac-

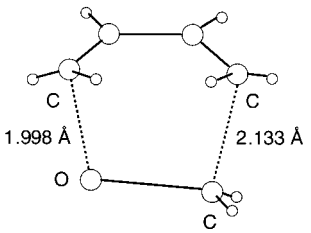

Fig. 8.12 Calculated transition-state structure for the hetero-Diels-Alder reaction of formaldehyde with butadiene [25 b]

tion. The transition state of the Lewis acid-catalyzed reaction has significant zwitterionic character, with a partial positive charge of 0.37 on the diene and a negative charge on the formaldehyde oxygen atom of –0.65 and –0.28 on BH_3. The coordination of the carbonyl oxygen atom to BH_3 makes the carbonyl group an acceptor of negative charge, and the O–B bond length in the transition state is 0.12 Å shorter compared with the BH_3–formaldehyde complex, indicating a tighter complexation in the transition state.

By coordination of the formaldehyde oxygen atom to BH_3 the activation energy of the reaction with 1,3-butadiene drops considerably. This is in agreement with the experimental results, since Lewis acid catalysis in general are required for reactions of carbonyl dienophiles to proceed [26] and/or are found to enhance the reaction rate. Houk et al. have found that, at the highest level of calculations (MP2/6-31G*), the activation energy is 8.9 kcal mol^{-1}, which is 12.0 kcal mol^{-1} lower in energy than the uncatalyzed reaction [25b]. The calculations indicate that the *exo* position is favored due to the greater electrostatic repulsion between BH_3 and butadiene fragment in the *endo* transition-state structure.

The mechanism for the hetero-Diels-Alder reaction of benzaldehyde **9** with the very reactive diene, Danishefsky's diene **10**, catalyzed by aluminum complexes has been investigated from a theoretical point of view using semi-empirical calculations [27]. The focus in this investigation was to address the question if the reaction proceeds directly to the hetero-Diels-Alder adduct **11**, or if **11** is formed via a Mukaiyama aldol intermediate (Scheme 8.4) (see the chapter dealing with hetero-Diels-Alder reactions of carbonyl compounds).

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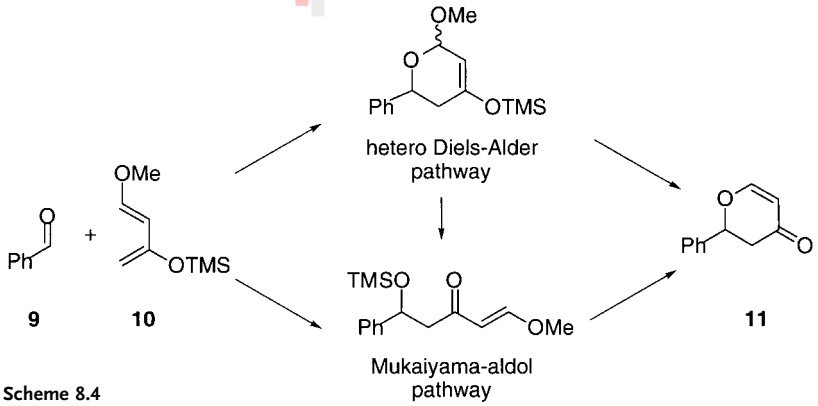

Scheme 8.4

The reaction was studied in the absence, and presence, of $(MeO)_2AlMe$ as a model catalyst for the BINOL-AlMe system. The change in relative energy for the concerted hetero-Diels-Alder reaction, and formation of the hetero-Diels-Alder adduct **11** via a Mukaiyama aldol reaction, is shown in Fig. 8.13. The conclusion of the study was that in the absence of a catalyst the concerted reaction is the most

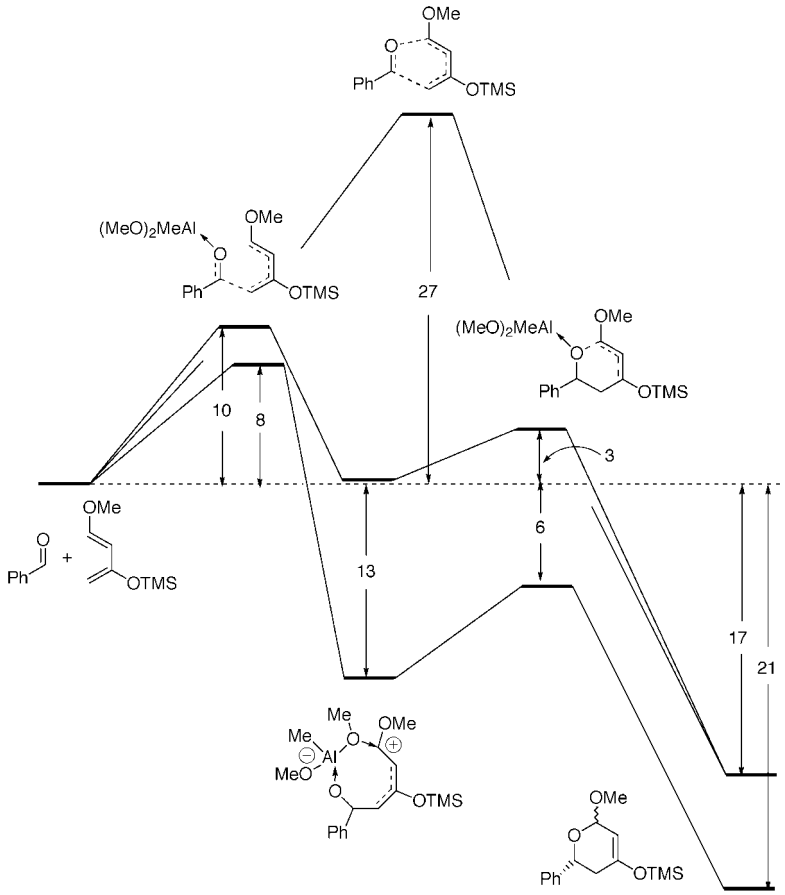

Fig. 8.13 Schematic representation of the change in energies for the concerted hetero-Diels-Alder reaction of benzaldehyde with Danishefsky's diene and the step-wise reaction in the presence of $(MeO)_2AlMe$ as the Lewis acid. Energies (kcal mol^{-1}) are relative to the total energy of the starting compounds [27]

likely one with a transition-state energy of 27 kcal mol^{-1}, while for the reaction catalyzed by $(MeO)_2AlMe$, a two-step mechanism is found with a transition-state energy of 13 kcal mol^{-1} for the first step (the C–C bond being formed) leading to the Mukaiyama aldol intermediate, followed by a 5 kcal mol^{-1} transition-state energy for the ring-closure step. The aldol intermediate seems to be stabilized by an interaction of the cation with the oxygen atom of the Lewis acid.

The structures along the reaction path in Fig. 8.13 are outlined in Fig. 8.14 starting with benzaldehyde activated by $(MeO)_2AlMe$ in the reaction with Danishefsky's diene **10** leading to the transition-state structure for the formation of the aldol-like intermediate, and finally the formation of the hetero-Diels-Alder adduct.

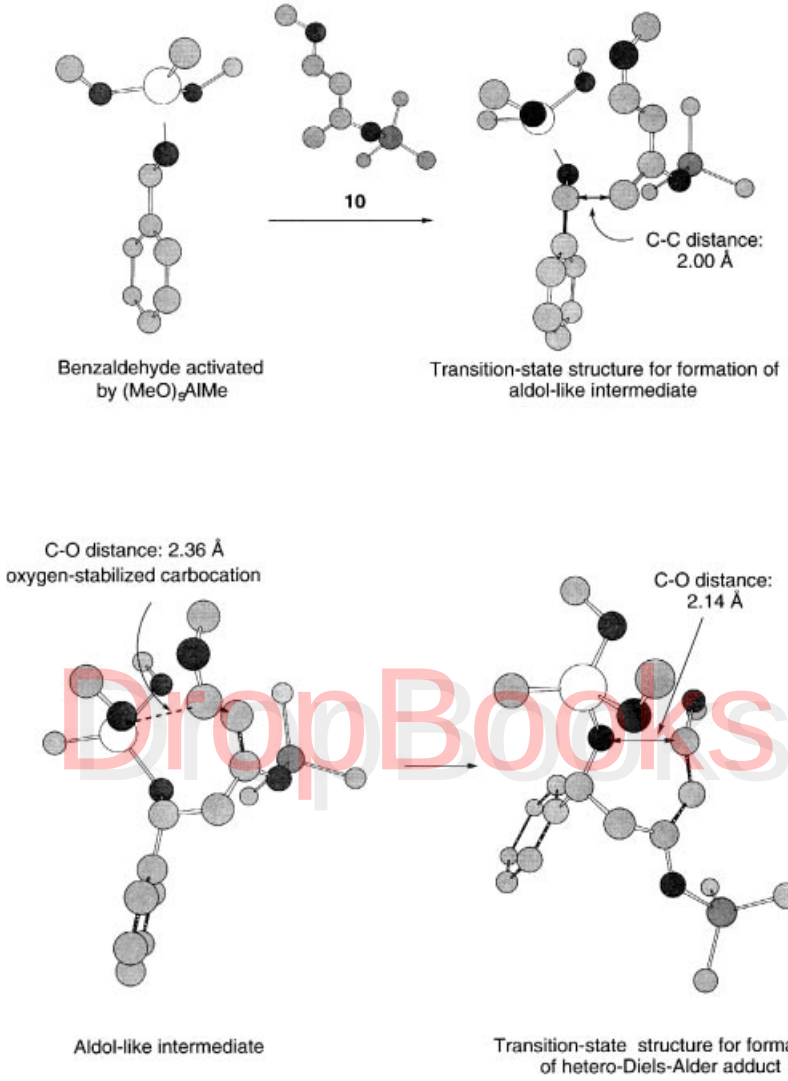

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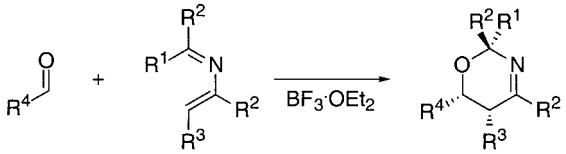
Fig. 8.14 The calculated transition-state structures along the reaction path for the step-wise formation of the hetero-Diels-Alder adduct **11** by reaction of benzaldehyde with Danishefsky's diene **10** [27]

The hetero-Diels-Alder reaction of aldehydes **12** with 2-azabutadienes **13** (Scheme 8.5) has been studied using high-level ab-initio multiconfigurational molecular orbital and density functionality calculation methods [28].

To determine the preferred pathway for the [4+2]-hetero-Diels-Alder reaction model reactions using formaldehyde (R^4=H for **12** in Scheme 8.5) as the carbonyl compound and 2-azabutadiene (R^1–R^4=H for **13** in Scheme 8.5) for the hetero



Scheme 8.5 **12** **13** **14**

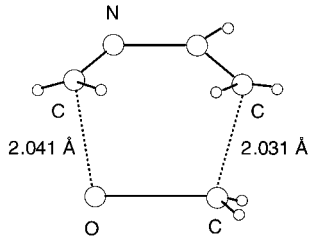


Fig. 8.15 Calculated transition-state structure for the [4+2] hetero-Diels-Alder reaction of formaldehyde with 2-azabutadiene [28]

diene. Both the concerted and stepwise reaction paths were calculated and the lowest energy transition-state structure for the uncatalyzed reaction is presented in Fig. 8.15 [28]. The basic feature for this transition-state structure is similar to those of transition-state structure located for similar reactions and show limited asynchronicity and the bond lengths being formed of about 2.0 Å. The three carbon atoms being involved in the bond formations are significantly pyramidalized. The calculated transition state energy for the uncatalyzed reaction is 17.2–47.6 kcal mol^{-1} depending on the basis set used. The transition state energy for the formation of the other regioisomer, and a step-wise reaction path, were found to be located higher in energy.

The transition state for the BH_3-catalyzed reaction was also found. The favored regioisomer and the influence of the Lewis acid on the reactivity was accounted for by a FMO-way of reasoning using as outlined in Fig. 8.11 to the left. The coordination of BH_3 to formaldehyde was calculated to lower the LUMO energy by 1.6 eV compared to formaldehyde, thus increasing the total charge transfer in the transition-state structure, which is calculated to be 0.377 at a RHF/6-31G* level of calculations. The presence of BH_3 as the Lewis acid for the reaction significantly increases the asynchronicity of the transition-state structures. For the *exo* transition-state structure, which has the lowest energy of the different transition-state structures located, the C–O and C–C bond lengths are calculated to be 2.368 and 1.904 Å, respectively, using the RHF/6-31G* basis set. The calculated transition-state structure energy for the BH_3-calculated reaction is calculated to be 8.1 kcal mol^{-1} at a Becke3LYP/6-31G* level of calculations, compared to 17.2 in the case of the uncatalyzed reaction. For this hetero-Diels-Alder reaction the theoretical results are in nice agreement with the experimental results [28].

8.3.3
Inverse Electron-demand Hetero-Diels-Alder Reactions

The final class of reactions to be considered will be the [4+2]-cycloaddition reaction of nitroalkenes with alkenes which in principle can be considered as an inverse electron-demand hetero-Diels-Alder reaction. Domingo et al. have studied the influence of reactant polarity on the reaction course of this type of reactions using DFT calculation in order to understand the regio- and stereoselectivity for the reaction, and the role of Lewis acid catalysis [29]. The reaction of e.g. nitroethene **15** with an electron-rich alkene **16** can take place in four different ways and the four different transition-state structures are depicted in Fig. 8.16.

For the uncatalyzed reactions the calculations showed that the *ortho* approaches were favored over the *meta*, and the *endo* selectivity was the energetic most favorable reaction paths for most of the electron-donating substituents studied [29]. The *endo-ortho* reaction path is under FMO control and the substituent effect on the regioselectivity was explained for by a dominant interaction between $LUMO_{diene}$ and $HOMO_{dienophile}$. The *ortho* reaction path was investigated with BH_3 as the Lewis acid and it was calculated that the presence of Lewis acid decreases the activation

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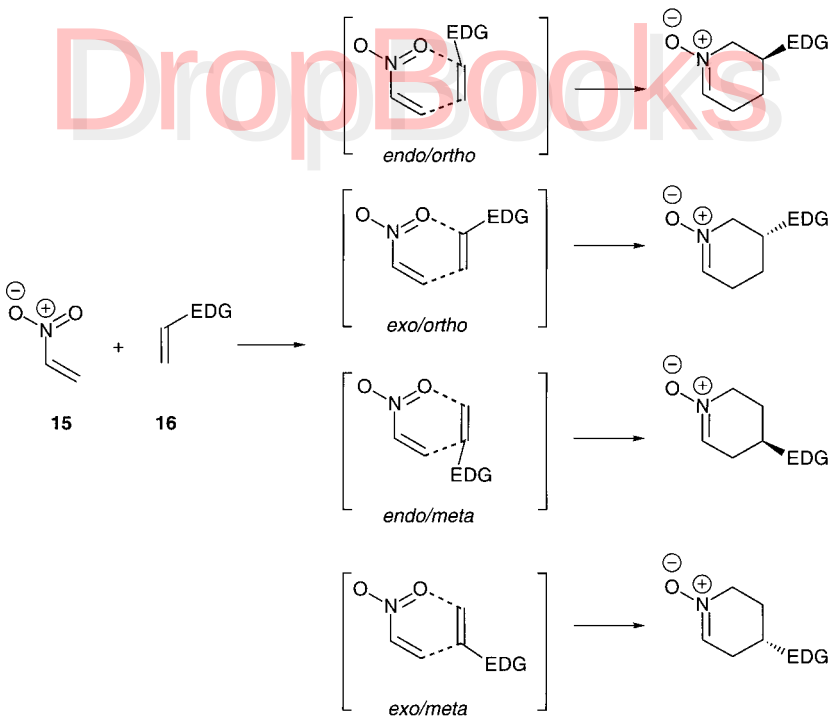


Fig. 8.16 The different approaches of an alkene substituted with an electron-donating group (EDG) to nitroethene

energy by 5.0–6.7 kcal mol^{-1} compared to the uncatalyzed reaction. The transition-state energies for the reaction of nitroethene with propene was reduced from 20.7 to 13.8 kcal mol^{-1} by coordination of BF_3 to the oxygen atom of nitroethene. The lower transition-state energy was explained in terms of a stronger interaction between the $LUMO_{diene}$ and $HOMO_{dienophile}$, as the LUMO energy of the BH_3-coordinated nitroethene was 0.78 eV lower compared to nitroethene (–2.60 eV). The BH_3 catalyst enhances the asynchronicity of the transition state due to an increase of the oxygen-carbon distance. However, the most notable effect of the Lewis acid as catalyst was the delocalization of the negative charge that being transferred in the transition state; the BH_3 fragment accepts 0.27 electron of the 0.31 electron transferred to the heterodiene system. It was stated that the role of the Lewis acid was to increase the electrophilic character of the nitroethene due to a stabilization of the corresponding transition-state structure through a delocalization of the negative charge that is being transferred along the nucleophilic attack of the substituted ethene [29].

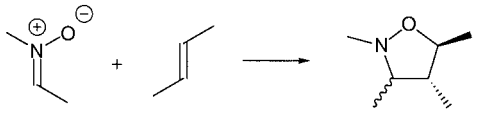
The number of theoretical investigations of hetero-Diels-Alder reaction is very limited. The few papers dealing with this class of reactions have shown that the influence of the Lewis acid on the reaction course can to a high extent be compared to those found the carbo-Diels-Alder reactions. At the present stage of investigations, however, more work is needed if we are to understand the influence and control of selectivity in Lewis acid-catalyzed hetero-Diels-Alder reaction – we are probably at the beginning of a new era in this field.

8.4
1,3-Dipolar Cycloaddition Reactions of Nitrones

The 1,3-dipolar cycloaddition reaction of nitrones with alkenes gives isoxazolidines is a fundamental reaction in organic chemistry and the available literature on this topic of organic chemistry is vast. In this reaction until three contiguous asymmetric centers can be formed in the isoxazolidine **17** as outlined for the reaction between a nitrone and an 1,2-disubstituted alkene. The relative stereochemistry at C-4 and C-5 is always controlled by the geometric relationship of the substituents on the alkene (Scheme 8.6).

8.4.1
Frontier-orbital Interactions for 1,3-Dipolar Cycloaddition Reactions of Nitrones

The relative FMO energies of the substrates of the 1,3-dipolar cycloaddition reaction of nitrones are important for catalytic control of the reaction. For the normal electron-demand 1,3-dipolar cycloaddition reactions the dominant FMO interac-



Scheme 8.6 **17**

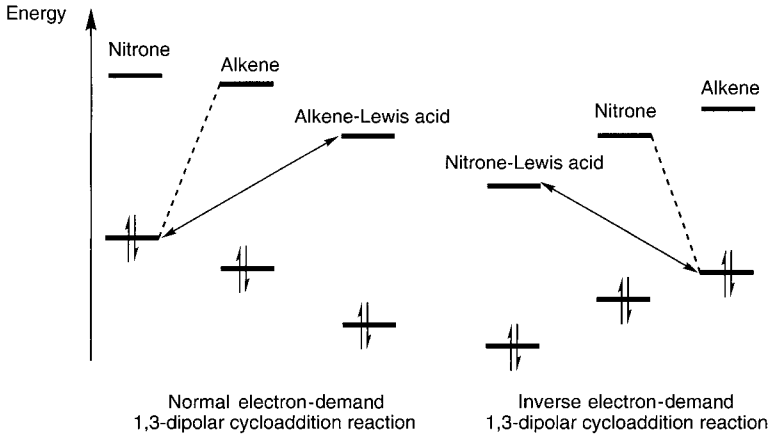


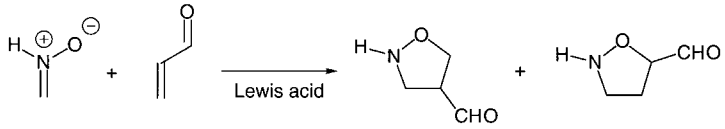
Fig. 8.17 An FMO diagram of the normal and inverse electron-demand 1,3-dipolar cycloaddition reactions of a nitrone with an alkene, in the absence and the presence of a Lewis acid

tion is that of the $HOMO_{nitrone}$ with the $LUMO_{alkene}$ as outlined to the left in Fig. 8.17. The inverse electron-demand 1,3-dipolar cycloaddition reactions are dominated by the interaction between the $LUMO_{nitrone}$ and the $HOMO_{alkene}$. By the application of a Lewis acid, the LUMO energy of the alkene is lowered by coordination of, e.g., the α,β-unsaturated carbonyl to the Lewis acid. As a result of the decreased energy gap between the interacting FMOs a rate acceleration of the reaction is achieved as shown to the left in Fig. 8.16. While for the inverse electron-demand 1,3-dipolar cycloaddition reaction of nitrones with electron-rich alkenes the application of Lewis acids will lower the LUMO energy of the nitrone and thus a more feasible interaction with the alkene becomes possible as schematically outlined to the right in Fig. 8.17 [30].

One of the problems related to the Lewis acid activation of α,β-unsaturated carbonyl compounds for the reaction with a nitrone is the competitive coordination of the nitrone and the α,β-unsaturated carbonyl compound to the Lewis acid [30]. Calculations have shown that coordination of the nitrone to the Lewis acid can be more feasible than a monodentate coordination of a carbonyl compound. However, this problem could be circumvented by the application of alkenes which allow a bidentate coordination to the Lewis acid which is favored over the monodentate coordination.

8.4.2 Normal Electron-demand Reactions

The Lewis acid-catalyzed 1,3-dipolar cycloaddition reaction of nitrones to α,β-unsaturated carbonyl compound in the presence of Lewis acids has been investigated by Tanaka et al. [31]. Ab-initio calculations were performed in a model reaction of the simple nitrone **18** reacting with acrolein **1** to give the two cycloadducts **19** and **20** (Scheme 8.7).



18 1 19 20

Scheme 8.7

The uncatalyzed reaction was calculated to give isoxazolidine **19** as the preferred regioisomer with a transition-state energy of 25.7 kcal mol^{-1} for the formation of the *exo* diastereomer [31]. Two types of catalytic reactions were investigated; first acrolein **1** was activated by coordination to BH_3, followed by coordination of the nitrone **18** to BH_3. The change in energy for the reaction of these two reactions are shown in Fig. 8.18 and compared with uncatalyzed reaction. The coordination of the Lewis acid to **1** and **18**, respectively, lower the energy of the reactants by 8.2 and 19.3 kcal mol^{-1}, with the nitrone-BH_3-acrolein system as the most stable combination. The calculated energies show that the 1,3-dipolar cycloaddition is most feasible by coordination of the Lewis acid to acrolein as the transition-state energy for this reaction is calculated to be 16.7 kcal mol^{-1}, compared to 30.4 kcal mol^{-1} for the reaction starting with the nitrone coordinated to BH_3. In the latter case, which in principle is a 1,3-dipolar cycloaddition reaction with inverse electron-demand (vide infra), the reaction is rather deactivated compared to the uncatalyzed 1,3-dipolar cycloaddition reaction. The most favorable transition-state structure shows that the coordination of the carbonyl oxygen atom of acrolein to BH_3 makes the carbonyl oxygen atom more electron-withdrawing so that the β-carbon atom becomes more electrophilic. This electronic change of acrolein is reflected in the transition-state structure of the reaction as the O–C bond is reduced from 1.85 Å in the uncatalyzed reaction to 1.59 Å in the Lewis acid-catalyzed reaction, while the C–C bond is increased from 2.35 Å to 2.57 Å. The use of more a stronger Lewis acid (BF_3) as the catalyst for the reaction shows that the 1,3-dipolar cycloaddition reaction leads to a step-wise reaction path taking place via, initially, the formation a Michael-adduct complex intermediate, followed by the ring-closure step. In the Michael-adduct complex the O–N and C–C bond lengths are calculated to be 3.04 Å and 1.53 Å, respectively; i.e. the stronger Lewis acid polarize the α,β-unsaturated carbonyl compound further which leads to the change in reaction path in the initial phase of the reaction.

8.4.3
Inverse Electron-demand Reactions

The other catalytic approach to the 1,3-dipolar cycloaddition reaction is the inverse electron-demand (Fig. 8.17, right), in which the nitrone is coordinated to the Lewis acid, which for the reaction in Scheme 8.7 was found to be deactivated compared to the uncatalyzed reaction. In order for a 1,3-dipolar cycloaddition to proceed under these restrictions the alkene should be substituted with electron-donating substituents.

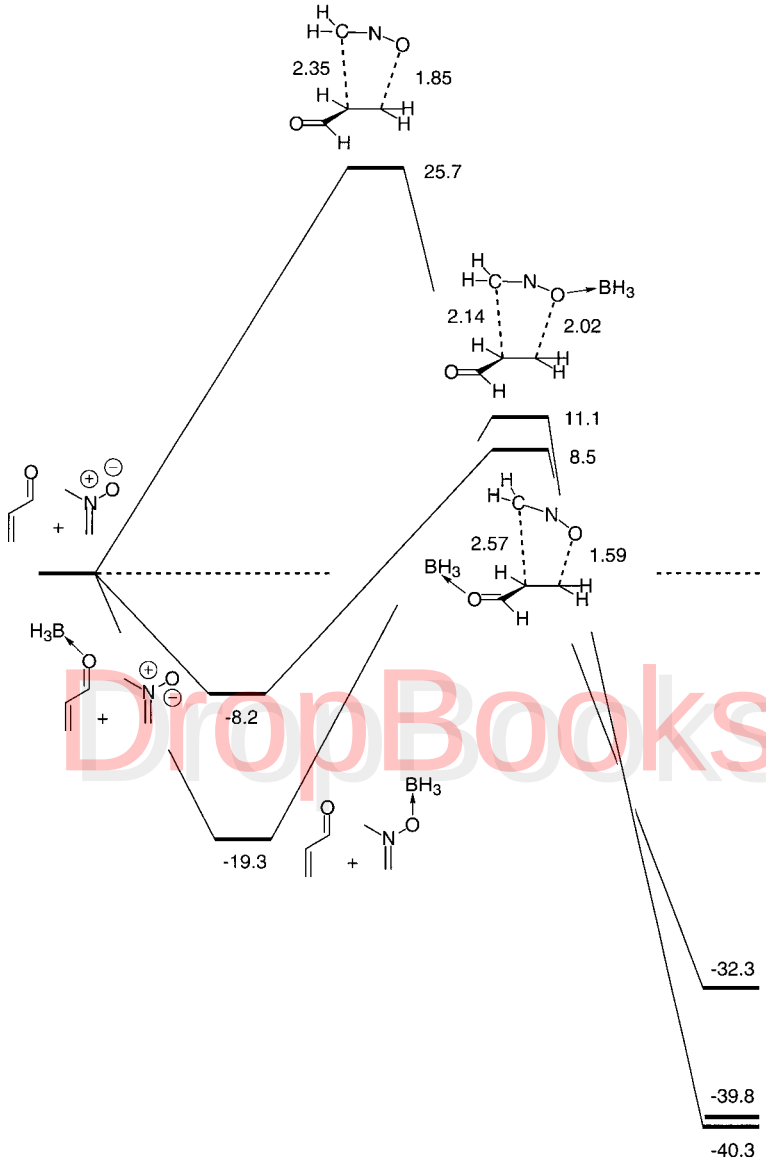


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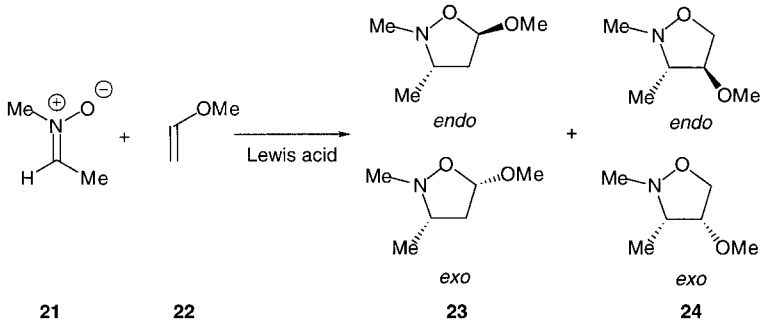
Fig. 8.18 Energy profile for the 1,3-dipolar cycloaddition reaction of the nitrone **18** with acrolein **1** under uncatalyzed reaction conditions, and in the presence of BH_3 as the Lewis acids. Energies (kcal mol^{-1}) are relative to the total energy of the starting compounds and bond lengths are in Å [31]

This reaction has been investigated by Domingo [32] using DFT calculations for the reaction of the dimethyl nitrone **21** with ethyl vinyl ether **22** (Scheme 8.8). The uncatalyzed reaction was calculated to proceed with formation of the *ortho*

compounds **23**, because of the lowest activation energy, ca. 14 kcal mol^{-1} (depending on the *exo*/*endo* selectivity) and being the most exothermic reaction of ca. 27 kcal mol^{-1}, which is ca. 8 kcal mol^{-1} and ca. 6–9 kcal mol^{-1} lower in energy compared to the reaction path leading to the *meta* compounds **24**. The difference in activation enthalpy for the formation of *endo*-**23** and *exo*-**23** is <1 kcal mol^{-1} with the lowest activation for the *exo* stereoselection, which is opposite to the calculations by Houk et al. [33] who found a 0.8 kcal mol^{-1} difference for the two transition states. It was pointed out by Domingo [32] that the relative low energy difference for the transition states agrees with the fact that the *endo*/*exo* selectivity for these 1,3-dipolar cycloaddition reactions depends on the bulk of the substituents present on both the nitrone and the substituted alkene.



Scheme 8.8

The Lewis acid-catalyzed reaction of nitrone **21** with ethyl vinyl ether **22** (Scheme 8.8) was also investigated for BH_3 and $AlMe_3$ coordinated to **21** [32]. The presence of BH_3 decreases the activation energy for the formation of **23** by 3.1 and 4.5 kcal mol^{-1} to 9.6 kcal mol^{-1} for the *exo*-selective reaction and 11.6 kcal mol^{-1} for the *endo*-selective reaction, respectively, while the activation energy for the formation of **24** increases by >1.4 kcal mol^{-1}, compared to those for the uncatalyzed reaction. The transition-state structure for the BH_3-*exo*-selective 1,3-dipolar cycloaddition reaction of nitrone **21** with ethyl vinyl ether **22** is shown in Fig. 8.19.

The influence of the Lewis acid catalyst can be understood from the FMO diagram to the right in Fig. 8.17. The Lewis acid catalyst enhances significantly the asynchronicity of the bond-forming process for the more favorable *ortho* transition state as the O–C distance in the BH_3-catalyzed reaction is 2.478 Å compared to 2.284 Å in the uncatalyzed reaction. For the use of $AlMe_3$ as the catalyst the O–C distance is calculated to be 2.581 Å in the transition state.

The role of the Lewis acid in these inverse electron-demand 1,3-dipolar cycloaddition reactions can be accounted for by an increase in the electrophilic character of the nitrone by the coordination to the Lewis acid. This gives a stabilization of the corresponding transition state by delocalization of the negative charge that is being transferred along the asynchronous cycloaddition process. The role of the Lewis acid on the regioselectivity the *ortho* selectivity is favored by charge transfer

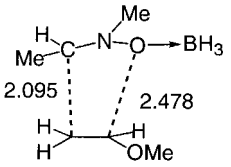


Fig. 8.19 The calculated transition-state structure for the BH_3-*exo*-selective 1,3-dipolar cycloaddition reaction of nitrone **21** with ethyl vinyl ether **22** [32]

by the presence of the nitrone oxygen atom, which stabilizes the incipient positive charge that is developed on the carbon atom of the substituted alkene during the cycloaddition process.

The theoretical investigations of Lewis acid-catalyzed 1,3-dipolar cycloaddition reactions are also very limited and only papers dealing with cycloaddition reactions of nitrones with alkenes have been investigated. The Influence of the Lewis acid catalyst on these reactions are very similar to what has been calculated for the carbo- and hetero-Diels-Alder reactions. The FMOs are perturbed by the coordination of the substrate to the Lewis acid giving a more favorable reaction with a lower transition-state energy. Furthermore, a more asynchronous transition-structure for the cycloaddition step, compared to the uncatalyzed reaction, has also been found for this class of reactions.

8.5 Summary

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The investigation of the metal-catalyzed cycloaddition reactions is in its beginning. We now begin to have the computational methods necessary for doing reliable calculations on systems being used in the laboratory. This chapter has shown that the one now begin to understand cycloaddition reaction from a theoretical point of view. There is, however, still a long way to go before computational chemists begin to understand and predict catalytic enantioselective cycloaddition reactions.

Acknowledgments

This work was made possible by a grant from The Danish National Research Foundation.

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